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INITIAL STABILIZATION OF THE DIABETIC CHILD

LIEUTENANT COMMANDER JOHN MITCHELL BRUSH (MC), U.S.N.R.

Throughout several years' observation the uniformity of the clinical response of children with diabetes mellitus to the treatment of the initial episode of glycosuria has been brought forcibly to our attention. Such uniformity is attained, to be sure, only when certain therapeutic policies and practices are observed. When this is done, however, the course of one patient conforms so closely to that of the next that it has been possible to predict that in the majority of instances, irrespective of the condition of the patient when treatment is begun, a previously untreated diabetic child will be discharged from the hospital within twenty-two to thirty days after admission on an adequate, "normal" diet, in a stable state, free from glycosuria and from hypoglycemic shock and requiring a single daily injection of 2 to 8 units of regular insulin. The regimen by which these results are achieved will be described later in this paper.

The development of a therapeutic program applicable to patients of various ages and with different degrees of ketosis and hyperglycemia grew out of the initial effort to simplify the management of diabetic children by holding certain potential variables relatively constant—namely, diet and the amount of muscular exercise permitted—while manipulating as a single variable the quantity of insulin administered in each twenty-four hours. This approach to the problem presently led to the discovery that the amount of insulin required to render the patient's urine free of sugar would within a week or so go beyond this point and evoke insulin shock. Progressive reduction of the daily dose of insulin then became mandatory, and it was soon found that the amount of insulin administered could be diminished each day at such a rate as to keep the urine free of sugar and yet protect the patient from violent manifestations of shock. Eventually, with the daily requirement of insulin reduced to something less than 10 units, the end of the adaptive process would be reached, and further reduction of the amount of insulin administered or elimination of insulin therapy usually could not be achieved without reappearance of glycosuria. When the amounts of insulin administered daily were plotted against time, some variation was found in the interval between the institution of treatment and the downward deflection of the curve which marked the reduction consequent to the first manifestation of insulin shock, but from the point of this deflection to the attainment of a stable level of insulin requirement the slopes of different curves paralleled one another with surprising uniformity. With further observation of individual patients after they were discharged from the hospital it became apparent that for a few weeks to several months they could be kept essentially free of glycosuria and of shock by the use of a constant daily dose of insulin, in other words, that they had achieved a steady state of production of endogenous insulin which required supplementation by only small amounts of exogenous insulin in order to maintain normal metabolism.

The condition which we have referred to as a steady state is not expected to last indefinitely. Juvenile diabetes tends to be severe, and it is recognized that within a year or two after the onset of symptoms most patients will come to require more than 30 units of insulin a day, and many of them far more, regardless of the methods by which they are treated in the early months after the onset. The regimen which we have adopted is therefore not expected to modify the long term result. However, by contrast with a number of other methods of treating diabetic children, it seems to possess certain clearcut advantages in that it holds the patient under close observation until he has reached a steady state, in that within this limit it confines him to the hospital a minimal length of time and in that it stabilizes his requirement of insulin at the lowest level compatible with efficient metabolic economy.

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PRINCIPLES OF THE METHOD AND PRACTICAL APPLICATION

The broad principles of the treatment to be described embrace the following considerations: During the period of stabilization, immediately following the diagnosis of diabetes mellitus, the child's dietary requirements can be satisfactorily computed on the basis of his age and weight. A diet so calculated can be expected to be taken well as soon as the patient completely recovers from the initial ketosis or even earlier; hence this feature of treatment ceases to be a variable. Hunger which develops during the adaptive period, after the disappearance of significant glycosuria, apparently represents a symptom of hypoglycemia rather than a true need for more food, and, in the interests of the patient's welfare, it is not allowed to lead to an increase in caloric intake. The approach to the patient's requirement of insulin is made boldly and with a view to eliminating glycosuria as rapidly as this can reasonably be done. The higher the total daily dose of insulin can be kept without untoward manifestations, the lower will be the final requirement, after the phase of recovery. After six to ten days during which the patient has been receiving a constant diet and the regulating dose of insulin has been determined and then maintained, improvement, manifested by shock, sets in. The amount of insulin administered is then decreased at a prescribed rate, which is calculated to steer the patient through the relatively narrow channel between glycosuria and insulin shock during the ensuing days of improving tolerance to carbohydrates and diminishing requirements of insulin. Mild shock, which is rarely disturbing to the child and never actually harmful, serves to indicate that enough insulin is being given. Improvement, once it has set in, may be terminated if the daily dose is reduced too abruptly because of the occurrence of severe shock; one loses ground by attempting to reduce the amount of insulin used as an end in itself.

TABLE 1.—*Caloric Requirement of Diabetic Children, Calculated According to Age and Body Weight*

Age, Yr.	Calories per Kilogram Daily
2	80 to 100
5	70
7	65
10	55
12	40 to 50

These principles and anticipated results apply to the management of children only. Newburgh [1] stated in 1941 that he was coming to believe more and more that diabetes in children and in adults represent two diseases, not one. There is more than sufficient evidence to support this viewpoint.

The practical application of the method is described in the following six steps, the first two having to do with regulation of diet and the last four with treatment with insulin. It must be emphasized that this regimen can be carried out only under the control provided by hospitalization. The program is instituted at the time of the patient's admission if he is in condition to accept it or within forty-eight hours if ketosis has been severe.

Step 1.—The total daily caloric requirement is calculated from table 1 on the basis of the age and weight of the patient.

In determining the diet for a given child the figure derived from the table is raised or lowered if his nutritional status clearly requires such divergence from the average. Such variation from the standard should be of small magnitude.

Step 2.—The details of the diet corresponding to the calculated total caloric requirement are derived from tables 2 and 3.

Diets appropriate for children have been calculated for each hundred calories from 800 through 2,200 daily. The basis for the distribution of calories among carbohydrates, proteins and fats in the diets tabulated has been the average consumption of healthy American children, the aim being to offer the patient palatable food in readily acceptable proportions of the ingredients. Table 2 lists the total number of grams of carbohydrate, protein and fat for each hundred calory level and the corresponding number of grams of each food for each of the five meals. Table 3 lists the groups of food referred to in table 2 and the groups of substitutes. From these two tables the entire diet can be prepared. Milk, in moderate amounts, is given at 10 a. m. and at 3 p. m. to offset the hypoglycemic effect of the preceding doses of insulin; other foods might be utilized for the same metabolic effect. While intermeal milk in ordinary pediatric practice often has a depressing effect on appetite, in the management of the diabetic child it is useful in controlling the desire for more food than his needs dictate.

The remaining carbohydrate of the diet is divided equally among the three chief meals. The protein and fat are fairly equally distributed. The noon meal and evening meal are interchangeable. The values for vegetables and fruits and for substitute foods are calculated in the usual manner. Essentially no attempt is made to cater to the child's dietary whims, since capriciousness of appetite is seldom found in diabetic children. Refusal of a small part of the diet calls for no

1. Round Table Discussion on Diabetes, J. Pediat. 20:782, 1942.

compensatory substitution, but if most of a meal is refused approximate replacement of the carbohydrate is made.

Step 3.—The initial daily requirement for insulin is calculated; the number of units is numerically equal to two thirds of the number of grams of fat in the diet.

Regular insulin or crystalline zinc insulin is employed in this regimen, and the two forms may be used interchangeably. The speed of the physiologic action of these forms of insulin corresponds to the tempo of the dietary hyperglycemic effect. Precipitated insulin and some of the newer insulin-protein combinations are useful in later management, but their slow and inconstant action renders them unsuitable for use when accurate control is essential and when day by day change is characteristic, as in the early course of the disease. Control which is sufficient for later maintenance may not be adequate for the attainment of maximal early recovery.

The numerical index given—the number of units of insulin required daily equals two thirds of the number of grams of dietary fat—should not be interpreted as a suggestion that the primary function of insulin is to aid in the combustion of fat. As will be seen from the manner in which the diet is calculated, the ultimate points of reference are the age and the weight of the patient; the justification for the formula cited lies in its simplicity and in its practical success. Take as an example a patient whose dietary requirements are calculated to be 1,800 calories; table 2 shows that the corresponding daily quota of fat is 90 Gm.; hence the total twenty-four hour dose of insulin is 60 units.

In approximately half of the trials the quantity of insulin so calculated will successfully regulate the condition of the patient. If the urine does not become virtually free of sugar within thirty-six hours the amount of insulin is raised by not more than 10 per cent daily until the glycosuria ceases. Shock is eliminated by reducing the dose not more than 10 per cent daily, and an even smaller reduction is advisable.

TABLE 2.—*Standard Diabetic Diets*

Total calories	800	900	1,000	1,100	1,200	1,300	1,400	1,500	1,600	1,700	1,800	1,900	2,000	2,100	2,200
Distribution, approximate number of grams															
Carbohydrate	70	80	85	100	110	120	135	145	155	165	175	190	200	215	240
Protein	40	45	50	50	55	60	60	65	70	70	70	75	80	85	85
Fat	40	45	50	55	60	65	70	75	80	85	90	95	100	100	100
Breakfast (7:30 a. m.)															
Fruit, 12% group	75	75	80	100	100	100	100	100	110	120	120	150	150	150	150
Cereal	10	10	10	15	15	20	20	20	20	20	20	20	25	30	30
Egg, not by weight	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Bread	..	..	..	..	..	..	10	15	20	25	30	30	30	30	45
Butter	5	5	5	5	5	5	5	10	10	15	15	15	20	20	20
Milk	100	150	150	150	150	150	150	150	150	150	150	150	150	200	200
Milk (10 a. m.)	100	100	100	100	150	150	150	150	150	150	150	150	150	150	150
Noon meal (12 noon)															
Meat	30	30	30	30	30	50	50	60	60	60	70	70	70	70	70
Potato	..	..	..	..	50	65	75	75	75	75	75	75	75	85	100
Vegetable, 3% group	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
Vegetable, 6% group	..	50	100	100	..	..	50	100	100	100	100	100	100	100	100
Bread	..	..	..	..	..	..	..	..	10	10	15	20	30	30	40
Butter	..	5	5	10	10	10	10	10	10	15	15	20	20	20	20
Milk	100	100	100	150	150	150	150	150	150	150	150	150	150	150	150
Fruit, 12% group	100	100	100	100	100	100	100	100	100	110	120	130	130	150	150
Milk (3 p. m.)	100	100	100	100	150	150	150	150	150	150	150	150	150	150	150
Evening meal (5 p. m.)															
Meat or substitute	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30
Potato or substitute	..	..	..	..	50	50	50	50	50	50	70	75	75	85	100
Vegetable, 3% group	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
Vegetable, 6% group	..	50	50	100	..	..	..	..	..	..	..	50	100	100	100
Bread	..	..	..	..	..	5	15	20	30	30	30	30	30	30	40
Butter	5	5	5	5	5	5	10	10	15	15	20	20	20	20	20
Milk	100	100	150	150	150	150	150	150	150	150	150	150	150	150	150
Fruit, 12% group	100	100	100	100	100	100	100	100	100	120	120	120	120	150	150

A fish oil concentrate containing vitamins A and D sufficient to supply at least 5,000 units of vitamin A and 500 units of vitamin D daily

The partition of the insulin administered during a period of twenty-four hours is important to the success of the regimen, the aim being to maintain the urine free of sugar at all hours of the day and night. This can be accomplished with four daily injections. As a matter of convenience in making the calculations, the 4 a. m. dose is determined first (step 4), after which the partition of the remainder of the day's insulin is more readily computed (step 5).

Step 4.—The 4 a. m. dose of insulin is determined from table 4.

Step 5.—After subtracting the 4 a. m. dose, the remainder of the total insulin is partitioned as four sevenths before breakfast, one seventh before the noon meal and two sevenths before the evening meal.

If the total daily dose of insulin is 60 units, the calculation is as follows: $60 - 4 = 56$; $56 \div 7 = 8$. Distribution of the doses of insulin is therefore ordered as 32-8-16-4.

Such an apportionment of the insulin appears to permit maximal recovery more constantly than do others and is regarded as essential to this regimen. Only exceptionally does one need to diverge from this distributive formula in order

TABLE 3.—*Groups of Foods According to Content of Carbohydrate*

3%	6%	9%
Asparagus	Eggplant	Beets
Broccoli	Green peppers	Brussels sprouts
Cabbage	Kale	Carrots
Cauliflower	Okra	Onions
Celery	String beans	Peas, canned
Cucumber	Turnips	Rutabagas
Mustard greens	Winter squash	
Radishes		
Romaine		21%
Sauerkraut	15%	
Spinach		Lima beans
Summer squash	Parsnips	Navy beans
Tomatoes	Peas, fresh	
Turnip tops		

Lettuce and mushrooms may be used as desired

Fruits, Fresh or Juice-Pack

6%	12%	15%
Cantaloup	Apricots	Apples
Honeydew melon	Cherries	Blueberries
Strawberries	Oranges	Grapes
Watermelon	Peaches	Pears, fresh
	Pineapple	
9%	Plums	21%
	Raspberries	
Grapefruit	Pears, canned	Bananas
Tangerines		

30%

Cooked dried apricots
Cooked dried prunes

Substitutes for Potato

Corn	Macaroni	Rice	Spaghetti

Lean Meats and Fish (Cut off All Visible Fat)

Beef	Liver	Cod	Haddock
Chicken	Turkey	Fillet of sole	Salmon
Lamb	Veal	Flounder	Scallops
		Halibut	

15 Gm. of bread may be substituted for 50 Gm. of potato
30 Gm. of cheese or one egg may be substituted for 30 Gm. of meat

TABLE 4.—*Guide to the 4 A. M. Insulin Requirement*

Total Daily Dose, Units	4 A. M. Dose, Units
0 to 20	0
21 to 30	1
31 to 40	2
41 to 50	3
51 to 60	4
61 and more	5

to control a tendency to shock at a constant hour of the day and then only by 2 to 4 units.

Insulin is administered one-half hour before breakfast, at the noon meal and either at or one-half hour before the evening meal. With this schedule shock is most likely to occur during the thirty minutes preceding one of the latter two meals.

Step 6.—When improvement, manifested by shock, sets in, after treatment for six to ten days, the total amount of insulin is reduced by 1 unit the first day, by 2 units the second day and then by 7.5 per cent of the original regulating dose daily until the 30 unit level is reached. Below the level of 30 units reduction is carried on according to table 5.

TABLE 5.—*Schedule for Administration of Insulin on Successive Days When Improvement Has Reduced the Daily Requirement Below 30 Units*

Insulin, Units				
	Distribution			
Daily Total	Before Breakfast	Noon	Before Supper	4 A. M.
28	16	4	8	0
25	15	3	7	0
22	14	2	6	0
19	13	0	6	0
17	12	0	5	0
15	11	0	4	0
13	10	0	3	0
11	9	0	2	0
9	7	0	2	0

For total amounts below 9 follow schedules A or B

A. If Initial Regulating Dose Was Above 40 Units

Before Breakfast	Noon	Before Supper	4 A. M.
7	0	0	0
5	0	0	0
3	0	0	0

B. If Initial Regulating Dose Was 40 Units or Less

Before Breakfast	Noon	Before Supper	4 A. M.
7	0	1	0
7	0	0	0
6	0	0	0
5	0	0	0
4	0	0	0
3	0	0	0
2	0	0	0

Within six to ten days after the regimen is started endogenous insulin begins to superimpose its action, producing manifestations of insulin shock, frequently about 11:30 a. m. or 4:30 p. m. The total dose of insulin is then reduced by 1 unit the next day and by 2 units the second day. Abrupt reduction slows or even terminates recovery. Prior to this period shock is viewed as evidence of the need for adjustment of the regulating dose. After six days of treatment signs of hypoglycemia are looked on as heralding the phase of recovery. The minimal reduction of the dose of insulin advocated for the first two days after shock is designed to insure that the patient has entered the phase of recovery sufficiently to keep pace with the scheduled reduction.

After this two day delay unquestioned improvement sets in. The daily dose of insulin is then reduced by 7.5 per cent of the established regulating dose. The amounts of insulin administered before the three meals are maintained in the 4:1:2 ratio. The 4 a. m. dose is lowered

in accordance with the changes in the total daily dose, as shown in table 4 until a total daily level of 30 units is reached. The 4 a. m. dose of insulin is then discontinued, and reduction of the daily quota is carried on at the rate of 3 units a day, as indicated in table 5. When the total daily quota of insulin is below 20 units the noon dose is dropped and the rate of reduction is slowed to 2 units each twenty-four hours. The end dose is arbitrarily determined as approximately 10 per cent of the original regulating level. Total daily amounts below 8 units are given as a single dose. If the original level was 40 units daily or less, reduction is slowed to 1 unit daily below the 10 unit level. The fixed schedule for reduction of the dosage of insulin below the 30 unit level is given in table 5.

During the period of metabolic recovery hunger must not be interpreted as representing an inadequacy in the number of dietary calories. The diet must not be increased. Hunger at this stage is a transient manifestation of recurring hypoglycemia and will disappear with the administration of a constant diet as reduction in the daily dose of insulin progresses. This regimen tends to anticipate improvement and hence to minimize the number of shocks. Insulin shock must be awaited, however, as the signal to initiate reduction of the amount administered daily. Shock rarely necessitates an acceleration of the rate of decrease in the amount of insulin administered. At the first sign of hypoglycemia part of the next meal or extra carbohydrate should be given promptly.

The evaluation of the adequacy of diabetic control during this entire period is made by determination of the urinary sugar. The kidney is constantly determining for us whether the level of the blood sugar is too high. This statement is especially true for children, in whom elevated renal thresholds for sugar are extremely uncommon early in diabetes and extreme fluctuation of sugar content in the blood is the rule. Isolated determinations of the blood sugar are no more than that, for the amount present during the minute when the specimen is taken is of no true value as a measure of the level during the remaining fourteen hundred and thirty-nine minutes of the day and night. For all practical purposes, control is adequate if the urine in four specimens, collected throughout periods terminating at the beginning of the meals and at midnight or 4 a. m., is mostly free of sugar with not above a 2 plus reaction at any time, that is, with not more than a moderate yellow precipitate with Benedict's solution. Isolated spills of several grams of sugar may have no significance if the subsequent specimens are free of sugar. Hyperglycemia reflected by isolated glycosuria may have been the result of an emotional upset or of a raid on a neighbor's tray. Consecutive spills mean trouble of some kind, usually infection or a more thorough technic in stealing. The regimen is modified accordingly. It is surprising how infrequently these spills occur.

Protection from cross infection and from opportunities for stealing would be afforded by keeping the patient strictly in bed. Activity, however, is so inherent a factor in the metabolic economy of a patient with diabetes that the children are allowed up as soon as the regimen is instituted.

CLINICAL MATERIAL

During the ten years from May 1931 through June 1941, 39 juvenile diabetic patients, previously untreated or treated for not longer than one week, were placed on the regimen described. All but 1 of them were admitted to the Babies Hospital. The 39 patients have been divided into five groups and numbered within each group approximately chronologically by the date of admission to the hospital.

Group 1 includes patients 1 to 21, all of whom followed a standard course, achieving stabilization within thirty days, with a daily insulin requirement of less than 10 units.

Group 2 includes patients 22 to 28, for whom the course of stabilization was prolonged but the insulin requirement attained was below 10 units.

Group 3 includes patients 29 to 33. Infection modified the course of recovery in these patients, but the end result was satisfactory except in 1 patient (no. 31) who did not remain in the hospital for complete stabilization.

Group 4 consists of patients 34 and 35, 2 children who weighed 11.2 and 10.1 Kg. and who showed unusually low early requirements for insulin.

Group 5, patients 36 to 39, represents four failures according to the standard established.

Classic acute diabetes mellitus in children rarely presents a diagnostic problem or leaves any room for doubt. With respect to the patients in this series the history, the presence of glycosuria with ketosis, in most instances the presence of hyperglycemia and in all instances the eventual clinical course adequately confirmed the diagnosis. In the 1 instance in which the history was not suggestive the level of the blood sugar and the subsequent course in response to insulin demonstrated unquestionable diabetes. With 1 exception the duration of symptoms prior to admission was fourteen weeks or less, the average being four and nine-tenths weeks. The one exceptional patient, no. 36, had definite symp-

toms, untreated, for a year; this patient is one of the 4 for whom the regimen was a failure.

Charts 1 and 2 show the total amount of insulin given to the patients of group 1 on successive days in the hospital. The records begin on the first day of full diet and insulin, usually within thirty-six hours after the admission of the

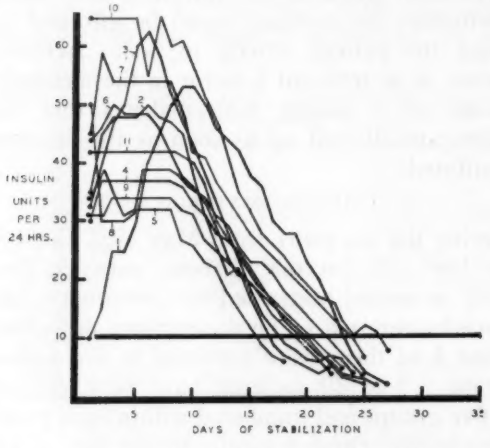

Chart 1.—The total daily dose of insulin on successive days for patients 1 through 11 of group 1 are plotted. The heavy line at the 10 unit level emphasizes the fact that all of the curves finally fall below this level. The curve for patient 3 is plotted at one-half the actual dose for each day, the maximum being 125 units on the sixth day, with a fall to 8 units on the twenty-second day.

patient. It is noteworthy that adjustment of the initial level of insulin is much more irregular in chart 1, which includes patients admitted up to March 1939, than in chart 2, which describes experiences at a time when the details of the regimen had become more clearly established. In chart 1 the curves for patients 9, 10 and 11 show the tendency toward flat initial plateaus, the single drop in the curve for patient 10 at six days representing an error in dosage. In chart 2 most of the variations from a smooth downward curve are fortuitous. The descending part of the curve for patient 12 presents three steps, representing unpremeditated irregularities in the amount of insulin administered which bore no relation to the patient's symptoms and which resulted entirely from the slips which may occur in part from the delegation of responsibility for writing and carrying out orders. The patient was a 10 year old girl whose urine showed a 2 plus reaction for sugar on the second day and never more than a 1 plus reaction subsequently.

Vagaries of this kind are still further brought out in chart 3, which illustrates courses of recovery in which the results were delayed. The factors which might account for such delay beyond the thirty day limit are of considerable interest and significance.

Patient 22, aged 2 years, was chronologically the first in the entire series. Her weight was less than 10 Kg., and the distribution of insulin throughout each day did not conform to the present scheme. At the 31 unit level the distribution was 28-0-3-0. Minor spills and repeated shocks with the maximum dose point to the absence of the control desired, a circumstance which probably delayed the eventual achievement of stabilization with a schedule of 2-0-0-0 units of insulin.

Patient 23 was 15 months old. The carbon dioxide-combining power of his plasma on admission was 4.6 volumes per cent. Again the small body mass of the patient, 11.4 Kg., and our inexperience in this method of control in 1932 contributed to irregularities. These circumstances, together with a too rapid decrease of insulin below the 20 unit level, may have produced the delayed course.

Patient 24 was 6 years of age. There is no apparent explanation for the delay until the twelfth day in the initiation of the period of recovery for this patient. Her subsequent course was satisfactory, the curve of the daily requirement for insulin paralleling those of the patients in group 1. By the thirty-third day the urine was free of sugar when the patient received 6 units of insulin daily.

Patient 25 was 4 years old. Through an error in the interpretation of orders the partitioning of the quota of insulin for each twenty-four hour period was out of phase with the patient's diet from the fifth to the nineteenth day of treatment. For an ordered dosage of 22-8-11-4, she was given 4 units before breakfast, 22 units before luncheon, 8 units before the evening meal and 11 units, uncovered, at 4 a. m. To our great surprise she was relatively free of shock and her urine was relatively free of sugar. One might have predicted with confidence that she would show repeated, severe shock and almost constant 4 plus glycosuria. She did not, however, enter the phase of recovery until the more usual program for the administration of insulin was reinstituted, after which her requirements fell, in the usual manner, to 2 units.

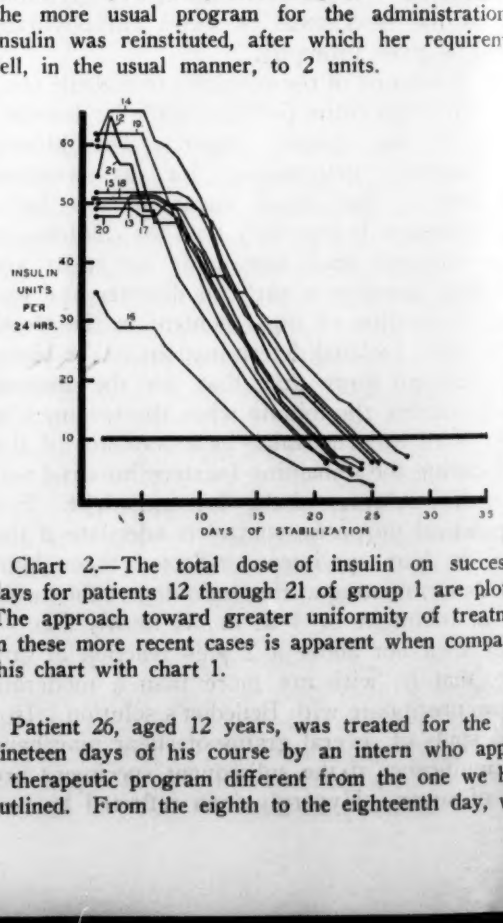

Chart 2.—The total dose of insulin on successive days for patients 12 through 21 of group 1 are plotted. The approach toward greater uniformity of treatment in these more recent cases is apparent when comparing this chart with chart 1.

Patient 26, aged 12 years, was treated for the first nineteen days of his course by an intern who applied a therapeutic program different from the one we have outlined. From the eighth to the eighteenth day, with

a dosage of 33-13-17-0 units of insulin, the patient was without glycosuria, free of shock and apparently well adjusted, under an adequate regimen. But he failed to demonstrate production of endogenous insulin at a time when his requirement of insulin should have been well on the downward course. Because of this delay, after readjustment of the dosage to 36-8-18-4 the amount of insulin administered daily was brought down carefully

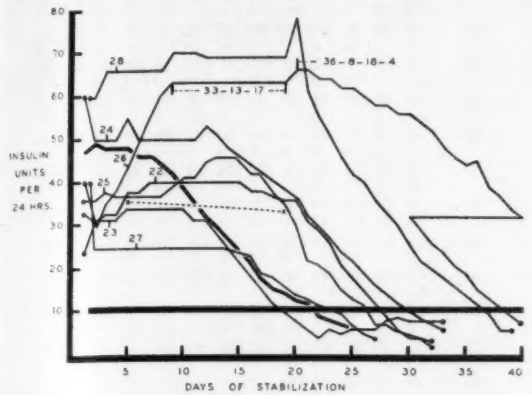

Chart 3.—The total doses of insulin on successive days for patients 22 through 28, comprising group 2, those with adequate but delayed response, are plotted. The single heavy curve represents the average response of the patients in group 1, excluding patients 1 and 3, children treated early in the years of the study, with an atypical rise in insulin requirement during the regulating period. The period during which the administration of insulin was out of phase with the diet for patient 25 is shown by the broken line between two x's. For patient 26 the period of administration of insulin during which the distribution differed from that of this regimen extended, as is shown, to the nineteenth day. The setback in the curve for patient 26 at forty days indicates that the end dose of insulin (7-0-0-0) was reached at fifty days.

to a single dose of 7 units before breakfast by the end of fifty days of treatment.

For patient 27, 6 years of age, the amount of insulin administered was drastically reduced on the first day of treatment by a member of the house staff, from the calculated dose of 40 units to 25 units, because the patient had shown shock. Reduction of this magnitude because of shock contravenes one of the basic principles of the regimen. Twenty-five units of insulin for this patient represents a ratio to dietary fat of 36 per cent. The patient's urine remained free of sugar and this dosage was therefore continued. Signs of improvement did not appear until the fourteenth day of treatment. The total stay in the hospital was not prolonged, and the final dosage was 4-0-0-0. The patient is included in group 2 because of the delay in initiation of the period of recovery.

Patient 28, 12 years of age, had a delayed course for which there is no obvious explanation beyond the fact that she showed an occasional elevation of temperature which was not traced to any known infection. She was discharged from the hospital, free of glycosuria with 6 units of insulin daily, after thirty-nine days of treatment.

The courses of patients comprising group 2 are thus instructive in that analysis clearly shows the cause of the delay for all but patients 24 and 28, in whose cases no adequate explanation was found. For these 2 patients the delay amounted to only three and nine days respectively beyond the limit of the period of recovery of the patients in group 1.

The influence of infection on diabetic tolerance requires no comment. Chart 4 outlines the courses of 5 patients who had significant infections. For 1 (patient 31) the end result of the regimen of treatment was unsatisfactory, but this patient was discharged after thirty-one days, with 12 units of insulin daily, before adequate stabilization could be effected. Chart 4 also shows the insulin curves for the 2 patients comprising group 4. The regulating dose of insulin for these patients was shown to be far below the calculated amount.

Patient 29, who was 2 years of age, had acute purulent otitis media at the time of admission to the hospital. After twenty-two days a subcutaneous abscess of the back was opened. Neither of these infections brought about any modification of the patient's course except for some spill and delay toward the end.

Patient 30, a girl 10 years of age, acquired an epidemic infection of the respiratory tract with fever after twenty-four days of treatment, just before the end of her expected period of recovery. After thirty-nine days she was free of glycosuria with 2 units of insulin daily.

Patient 31, a girl aged 7 years, contracted the same infection that patient 30 had acquired, after twenty-one days of treatment. She did not remain in the hospital for adequate stabilization.

Patient 32, a boy 2½ years of age, contracted otitis after twenty days in the hospital, followed by chronic tonsillar and adenoidal infection.

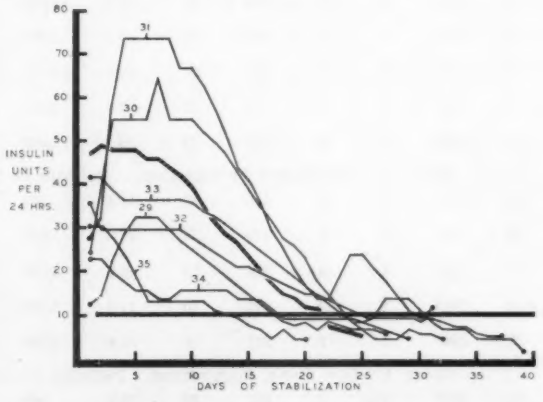

Chart 4.—The total doses of insulin on successive days for patients 29 through 33, comprising group 3, those whose course was modified by infection, and for patients 34 and 35, comprising group 4, those with a low early requirement, are plotted. The single heavy curve represents the average response of patients in group 1, exclusive of patients 1 and 3.

Patient 33, a boy 3 years old, had otitis media after twenty-three days of treatment.

Patients 34 and 35 weighed less than 1,200 Gm. each. Because of shock the regulating dosage of insulin was reduced to 36 per cent and 31 per cent of the dietary

TABLE 6.—*Pertinent Data for All*

Patient No.	Year of Admission	Age, Yr.	Duration of Symptoms, Wk.	Blood Sugar, Mg./100 Cc.	Blood CO_2, % by Vol.	Weight of Patient, Kg.	Diet: Calories	Diet: Cal./Kg.	Units of Insulin, % of Grams of Fat	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Group 1. Standard Course. Patients 1 to 21																							
1	1931	8	7	178	44	29.0	1,800	62	59	10	15	25	25	30	40	45	50	53	53	50	46	44	42
										78	55	47	43	38	4	4	1	0	0	0	0	2+	0
2	1931	5	3	278	44	18.4	1,300	71	74	35	45	48	48	48	50	48	47	45	38	31	26	21	22
										5	2	0	2+	2+	0	0	0	0	0	0	0	0	0
3	1932	13	3	468	14	40.5	2,100	52	125	65	80	95	100	120	125	117	104	95	86	76	66	56	46
										52	1	34	4	7	0	3+	0	2+	2+	0	0	0	0
4	1933	3	1½	256	35	15.7	1,100	70	67	30	37	37	37	37	37	37	36	33	31	28	27	25	
										2+	0	0	0	0	0	2+	0	0	0	0	0	0	
5	1933	2	4	357	34	12.4	1,000	81	64	34	39	35	31	32	32	32	32	27	26	23	22	18	15
										2+	4	2	0	1	0	0	4+	0	..	2	0	0	0
6	1933	8	0	197	..	22.2	1,400	63	69	44	46	50	48	48	48	46	42	38	36	33	28	24	21
										6	0	0	0	0	0	0	0	4	0	0	0	0	0
7	1936	12	6	484	38	29.8	1,600	54	68	45	59	54	54	54	54	54	48	42	41	37	34	31	
										26	0	5	0	0	0	0	0	0	0	0	0	0	
8	1936	6	2	508	11	18.5	1,200	65	65	50	30	30	30	32	39	39	39	38	36	34	31	29	25
										0	11	2+	10	0	0	0	0	0	0	0	0	0	0
9	1938	4	4	100	..	14.7	1,100	75	62	31	31	34	34	34	34	34	34	32	31	27	25	23	21
										0	3	0	2+	0	0	0	0	0	0	0	0	0	0
10	1937	8	3	210	58	29.1	1,800	62	72	65	65	65	65	65	55	65	60	61	56	51	46	41	35
										2+	0	0	4+	0	0	0	0	0	0	0	0	0	0
11	1939	5	3	110	..	16.2	1,200	74	70	42	42	42	42	42	42	42	41	40	36	30	27	24	
										0	0	0	0	4+	3+	0	2+	0	0	0	0	0	
12	1939	10	4	211	54	35.3	1,800	51	67	55	65	60	60	54	47	47	47	44	42	38	38	35	35
										0	2+	0	0	0	0	0	0	0	0	0	0	0	0
13	1940	11	5	496	32	28.7	1,700	59	59	50	50	50	50	50	50	49	47	44	40	36	32	29	26
										11	2	0	0	0	2+	0	0	0	0	0	0	0	0
14	1940	10	6	222	..	48.7	2,000	41	66	61	66	66	66	66	61	60	58	55	51	46	40	36	32
										2+	2+	0	0	0	0	0	0	0	0	0	0	0	0
15	1940	10	9	115	47	30.8	1,500	49	69	52	52	52	52	52	52	52	51	49	45	39	35	31	
										0	0	0	0	0	0	0	0	0	0	0	0	0	
16	1940	3	13	374	41	12.9	1,100	85	53	35	31	29	29	29	29	26	24	22	20	18	16	14	12
										0	0	0	0	0	0	0	0	0	0	0	0	0	0
17	1941	8	1½	400	13	22.3	1,500	67	67	50	50	50	50	48	48	50	50	50	49	47	43	39	35
										0	0	2+	2+	2+	2+	0	0	0	0	0	0	0	0
18	1941	9	2	682	21	24.1	1,500	62	68	51	51	51	51	51	51	50	49	44	41	37	33	29	26
										0	0	0	0	0	0	0	0	0	0	0	0	0	0
19	1941	8	6	320	53	40.2	1,800	45	69	62	62	62	62	62	57	52	47	42	38	33	29	26	23
										0	0	0	0	0	0	0	0	0	0	0	0	0	0
20	1940	13	1	458	53	46.7	2,200	47	51	48	48	48	51	51	51	50	48	44	40	36	32	28	25
										4+	2	11	0	2+	2+	0	0	0	0	0	0	0	0
21	1941	12	14	375	46	41.2	1,800	44	63	60	60	57	57	49	49	43	38	35	32	29	26	23	20
										0	0	0	0	0	0	0	0	0	0	0	0	0	0
Group 2. Delayed Good Results. Patients 22 to 28																							
22	1931	2	12	500	19	9.6	900	95	89	24	31	33	33	38	38	40	40	40	40	40	40	40	40
										17	34	13	3	4	2	1	1	0	2	1	1	0	0
23	1932	1¼	1	920	4.6	11.4	800	70	85	33	31	31	31	34	34	34	34	34	34	30	30	27	24
										0	0	2+	0	4+	0	0	0	0	2+	3+	4+	0	4+
24	1935	6	3	294	43	21.7	1,500	69	67	60	50	50	50	55	50	50	50	50	50	50	53	51	48
										2+	0	0	4+	0	0	0	0	0	0	0	0	0	0
25	1935	4	3	265	36	13.4	1,000	75	74	36	36	38	37	37	37*	37	37	39	41	41	44	45	45
										2+	5	0	2	0	2+	0	0	0	0	0	0	0	0
26	1939	12	9	150	..	43.5	2,000	46	66	40	30	35	38	43	49	55	60	63	63	63	63	63	63
										4+	4+	4+	4+	4+	4+	4+	0	0	0	0	0	0	0
27	1939	6	5	294	19	20.9	1,400	67	36	40	25	25	25	25	25	25	25	25	25	25	25	25	
										0	0	0	0	0	0	0	0	0	0	0	0	0	
28	1940	12	14	425	26	35.6	2,000	56	69	60	60	66	66	66	66	66	66	70	70	70	69	69	69
										4+	4+	4+	4+	0	4+	0	2+	0	0	0	0	0	0
Group 3. Complicated by Infection. Patients 29 to 33.																							
29	1933	2	6	440	13	11.4	900	79	73	13	15	23	29	33	33	33	30	27	25	23	21	19	17
										0	4	3+	0	0	0	0	0	0	0	0	0	0	0
30	1934	10	6	370	20	38.3	1,800	47	61	25	40	55	55	55	55	64	55	55	55	52	50	47	43
										15	33	16	0	4+	0	0	0	0	0	0	0	0	0
31	1934	7	4	322	18	25.6	1,600	63	92	28	32	59	74	74	74	74	74	67	67	63	58	52	44
										21	13	5	1	0	0	0	2+	0	0	0	0	0	0
32	1940	2	10	275	10	11.9	1,000	84	60	36	30	30	30	30	30	30	30	30	28	26	24	22	20
										0	0	0	0	0	0	0	0	0	0	2+	4+	0	0
33	1940	3	2	227	32	15.8	1,300	82	57	42	42	39	37	37	37	37	37	37	36	34	33	31	29
										0	0	0	0	0	0	0	0	0	0	3+	0	0	0
Group 4. Low Early Requirement. Patients 34 and 35																							
34	1940	1½	2	337	20	11.2	900	80	36	24	23	20	18	16	16	14	14	16	16	16	16	16	14
										4+	0	3+	0	0	0	4+	4+	0	0	4+	0	0	2+
35	1940	2	3	536	24	10.1	900	89	31	30	30	28	24	19	14	14	14	14	14	14	12	11	10
										0	0	0	0	0	0	0	0	0	0	0	0	0	0
Group 5. Failures. Patients 36 to 39																							
36	1932	11	52	484	26	30.0	1,800	60	78	25	40	54	65	70	70	67	61	58	54	50	47	47	44
										4+	49	15	3+	0	0	0	0	2+	0	0	0	0	0
37	1934	10	3	284	19	28.3	1,500	53	75	60	60	60	60	56	51	51	51	56	52	48	43	39	33
										17	6	0	11	2	2+	0	0	0	7	0	0	0	0
38	1935	4	3	54	45	13.8	1,200	86	80	45	45	45	46	48	44	44	48	48	48	48	48	48	48
										4+	5	0	0	0	0	0	0	0	0	0	0	0	0
39	1938	1¼	½	..	16	8.9	800	90	77	31	31	31	30	27	26	23	21	19	17	15	13	11	9
										0	0	0	0	0	2+	0	2+	0	2+	0	0	2+	0

* Insulin timing out of phase with diet from sixth to nineteenth days, inclusive.

Upper line of figures: Units of insulin, total dose.
Lower line of figures and signs: Urinary sugar, total grams in twenty-four hours or the most strongly positive qualitative reaction. A reaction of 1+ is recorded as 0.

Days of Stabilization

15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50
38	36	30	28	28	23	20	16	11	7	4	3	2	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
0	1	1	0	0	0	0	0	0	0	0	0	0																							
17	13	9	7	6	5	4	5	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
0	0	0	2+	0	0	2	0																												
36	28	23	18	16	13	10	12	11	8	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
5	11	2+	0	0	2+	2+	5	0	0																										
22	19	16	13	11	9	7	5	4	4	3	2	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
0	0	0	0	0	0	0	0	0	0	0	0																								
12	9	7	6	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
0	0	0	0																																
19	17	14	12	10	8	6	4	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
0	0	0	0	0	0	0	0																												
28	26	24	22	20	18	16	14	12	10	7	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
0	0	0	0	0	0	0	0	0	0	0																									
23	23	21	18	16	14	12	10	8	6	4	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
0	0	0	0	0	0	0	0	0	0	0																									
19	17	15	13	11	9	7	5	4	3	2	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
0	0	0	0	0	0	2+	2+	2+	0	0																									
32	28	26	24	21	19	17	16	13	10	12	11	8	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
9	0	2+	0	0	3	2+	0	0	9	2+	5	2+																							
22	19	16	14	12	10	9	7	5	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
4+	2+	2+	2+	0	0	0	0	0																											
33	30	30	25	23	21	19	17	16	14	12	10	8	7	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
0	0	0	0	0	0	0	0	0	0	0	0	0	0																						
23	20	18	16	14	12	9	7	6	5	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
0	0	0	0	0	0	0	0	0	0																										
28	24	21	18	18	16	14	12	10	8	6	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
0	0	0	0	0	0	0	0	0	0	0																									
29	26	23	20	19	16	14	12	10	8	6	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
0	0	6	0	0	0	0	0	0	0	0																									
10	8	7	6	5	5	5	4	3	3	2	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
0	0	0	0	0	0	3+	0	0	0	0																									
31	28	25	22	19	17	15	13	11	9	7	6	5	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
0	0	0	0	0	0	0	0	0	0	2+	0	2+																							
23	20	17	15	13	11	9	7	7	5	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
0	0	0	0	0	0	0	0	0	0																										
20	17	14	12	10	8	6	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
0	0	0	0	0	0	0																													
22	19	17	15	13	11	9	7	6	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
0	0	0	0	0	0	0	0	0																											
18	16	14	12	10	8	7	6	5	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	.
0	0	0	0	0	0	0	0	0																											
40	38	38	37	36	36	31	29	26	26	21	18	15	12	9	6	4	4	2	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
0	0	1	1	1	1	0	0	1	0	0	0	0	1	1	1	0	1	0																	
21	18	15	12	10	8	6	4	6	5	6	6	6	8	9	8	8	8	8	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
0	2+	0	0	0	0	4+	4+	0	4+	0	4+	0	0	3+	3+	0	0	0																	
46	44	42	40	38	36	32	30	27	24	22	19	16	14	12	10	8	7	6	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0																	
45	42	42	37	35*	30	22	21	19	15	13	11	7	7	6	5	4	3	2	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
0	4+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0																	
63	63	63	63	63	66	66	64	64	62	62	60	58	58	56	56	54	52	48	46	44	45	39	37	34	32	29	26	24	21	19	15	13	11	9	7
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
23	23	19	18	16	14	13	11	10	9	7	5	4	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
0	0	0	0	0	0	0	0	0	0	0	0	0																							
69	69	69	69	69	78	60	55	51	46	42	40	36	33	30	26	22	20	18	16	14	12	10	6	6	..	..	..	..	..	..	..	..	..	..	..
0	0	0	0	4+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4+	0											
17	15	13	11	9	8	9	7	9	8	7	7	7	6	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
0	2+	1	0	1	2	3	0	11	2+	0	0	0																							
43	39	35	32	28	26	23	18	15	12	9	9	10	14	14	14	11	9	7	7	7	5	5	5	5	2	..	..	..	..	..	..	..	..	..	..
0	0	0	0	0	0	0	0	0	0	2+	2	1	2+	0	0	0	0	0	0	0	0	0	0	0											
44	41	36	30	26	21	17	14	14	19	24	24	21	18	14	11	9	12	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
0	3+	0	0	0	0	5	14	10	4+	0	0	0	0	0	2+	8																			
20	20	19	18	17	16	15	15	14	13	12	11	10	10	10	10	10	9																		
0	0	0	0	0	0	0	0	0	2+	0	2+	2+	0	0	0	0	0																		
29	27	25	23	21	19	17	15	13	11	9	7	5	5	5	7	6	6	5	(R-3/P-2)																
0	0	0	0	0	0	0	0	0	2+	2+	4+	4+	4+	0	0	0	0																		
14	14	13	11	10	10	10	10	10	10	10	9	8	7	6	5	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
2+	0	0	0	2+	0	0	2+	0	0	0	0	0	0	0	0																				
10	8	7	5	7	5	5	5	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
0	0	4+	4+	2+	3+	0																													
44	41	38	35	33	29	27	26	21	18	15	12	9	20	18	18	18	22	25	26	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
0	0	0	0	0	0	0	0	0	0	4	0	5	2	6	2+	2	2+	0																	
38	28	23	21	23	23	30	30	30	..	..	..	..	..	..	..	..	..	..	0	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
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43	40	36	32	28	25	22	20	17	15	13	11	9	10	10	13	18	18	21	21	21	21	..	..	..	..	..	..	..	..	..	..	..	..	..	..
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9	2+	4+	4+	4+	4+	4+	4+	0	2+	4+	4+																								

fat respectively. The eventual decrease in the amount of insulin required by patient 34 was somewhat delayed. For patient 35 the reduction of the dosage of insulin was carried out too rapidly, within seventeen days, but the patient's urine subsequently became free of sugar after twenty-one days of treatment.

It is noteworthy that only 1 (patient 31) of the 35 patients in groups 1 to 4, despite errors, delayed treatment and infection, showed a "poor" result in the sense of failure to stabilize with a requirement for insulin of 10 units or less.

Chart 5 presents group 5, the 4 patients for whom the regimen of treatment failed in the series of 39 patients.

Patient 36, a girl 11 years old, had symptoms of diabetes for one year prior to admission to the hospital, but she said she had not received any treatment. The existence of the disease over a long period doubtless accounts for the failure of the patient to respond to the administration of insulin in a manner comparable to that of the rest of the patients.

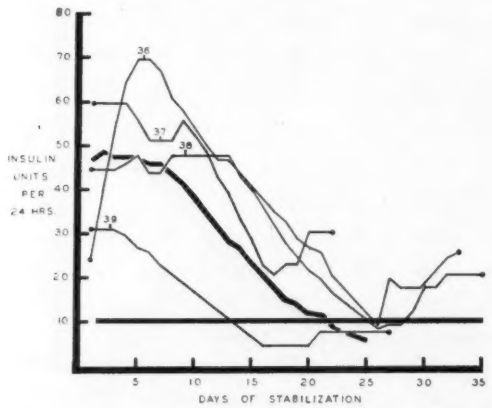

Chart 5.—The total doses of insulin on successive days for patients 36 through 39, comprising group 5, those who are classed as failures, are plotted. The single heavy curve represents the average response of patients in group 1, exclusive of patients 1 and 3.

For the failure of patient 37 to achieve the final daily requirement of 10 units or less of insulin there is no explanation. The patient was 10 years of age.

Patient 38, a girl 4 years old, except for some delay in initiating the phase of recovery, had a satisfactory course for twenty-four days, at which time she was free of glycosuria with 11-0-2-0 units of insulin. Then unexplained glycosuria occurred, which was controlled by 21 units of insulin daily. Nine days after the initial spill the patient's temperature rose to 102 F., and it remained elevated for five days. The child was discharged at the end of seventy days of hospitalization free of glycosuria with a dosage of 10-0-2-0 units of insulin.

For patient 39, aged 14 months, too rapid early reduction of the amount of insulin administered may have influenced the outcome. The patient was discharged from the hospital with 5 units of regular insulin and 3 units of protamine zinc insulin daily before breakfast.

Table 6 contains essentially all of the pertinent data concerning the 39 patients. The patients are listed in approximately the chronologic order of treatment within each of the five groups previously defined. Some of the factors analyzed deserve comment.

Date of Admission.—The date of admission for each patient is significant because the courses of the patients reported on formed the basis for the progressive development and formulation of the regimen described. The earlier courses therefore conform less closely to the planned program and are modified by deviations now avoidable.

Age.—The ages of the patients ranged from 14 months to 13 years. Since in a number of instances, especially during the earlier years of the study, the choice of the initial dosage of insulin was not so closely related to the weight of fat in the diet as was later found expedient, it is of interest to analyze the data for group 1 in order to determine whether any relationship exists between the patient's age and the ratio of insulin to dietary required for successful regulation. These figures are presented in table 7, from

TABLE 7.—*Ratio of Regulating Dose of Insulin to the Weight of Fat in the Diet*

Patient	Age, Yr.	Diet, Cal./Kg. of Body Weight	Insulin, Units/100 Gm. Dietary Fat
5	2	81	64
16	3	85	53
4	3	70	67
9	4	75	62
11	5	74	70
2	5	71	74
8	6	65	65
19	8	45	69
17	8	67	67
10	8	62	72
6	8	63	63
1	8	62	59
18	9	62	68
15	10	49	69
14	10	41	66
12	10	51	67
13	11	59	59
7	12	54	68
21	12	44	63
3	13	52	125
20	13	47	51

which it may be concluded that the ratio is not modified by differences in the ages of the patients.

Duration of Symptoms.—Diabetes in childhood is an acute disease, which progresses rapidly to the point at which treatment becomes necessary. Excluding patient 36, in whom symptoms had been present for one year, the first symptom attributable to diabetes antedated admission to the hospital by an average interval of four and nine-tenths weeks, with a maximum of fourteen weeks.

Blood Sugar.—The value shown for blood sugar is the first recorded determination, usually the level found at the time of admission of the patient to the hospital. Patients 9, 11 and 38 had 100, 110 and 54 mg. of sugar per hundred cubic centimeters of blood respectively. These were fasting levels, determined the morning after the admis-

sion of the patient and after two or more injections of insulin. The record for patient 15, however, represents the earlier stages of the disease, when the patient shows severe glycosuria after meals but is still capable of eliminating the hyperglycemia during a night's fast. This previously untreated girl of 10 years was admitted at 3 p. m., at which time her urine showed a 4 plus reaction to Benedict's test. Without benefit of insulin, the midnight to 8 a. m. partition specimen of urine gave a 2 plus reaction for sugar. The fasting level of the blood sugar was 115 mg. per hundred cubic centimeters. The patient was given 52 units of insulin daily, and for the next seven days she was free of shock and of glycosuria. Her ability to eliminate sugar in the fasting state did not modify the ratio of insulin to dietary fat of 69 per cent. Her carbohydrate-regulating mechanism apparently accepted essentially complete substitution of exogenous insulin for endogenous insulin.

Carbon Dioxide–Combining Power of the Plasma.—The values found for combining power ranged from 4.6 to 58 volumes per cent. Ketosis does not delay the patient's improvement as shown by the slope of the curve for the amount of insulin required. Severe ketosis at the time the patient is admitted to the hospital cannot be incriminated as a cause of failure to respond with a satisfactory diminution in the amount of insulin required.

Weight.—The patient's weight at admission to the hospital is given since it is the one from which the total number of calories in the diet was calculated. In the present series the range extended from 8.9 to 48.7 Kg.

Calories.—The details of the diet offered to the individual patients can be reconstructed with essential accuracy from the figures given in tables 6, 2 and 3. Although the last-mentioned tables are given in the revised form of June 1941, the changes made from previous dietary lists are believed to be of no significance.

Calories per Kilogram.—The variations from the standards for dietary calories per kilogram of body weight, shown in table 1, have been discussed.

Ratio of Insulin to Dietary Fat.—Step 3 of the regimen as outlined earlier describes the presumed requirement of insulin for initial regulation as two thirds, 67 per cent, of the number of grams of fat in the diet. The ratios of insulin to fat presented in table 6 differ in many instances from this mean value, the lowest being 31 per cent and the highest 125 per cent. No significant correlation is found between the ratios and the ages of the patients. The regimens for earlier patients show a considerable range of these ratios on both sides of the mean, reflecting the fluid state of the therapeutic concept in those times. Departures from the average ratio in more recent instances were determined by the individual patient's response, the twenty-four hour dose of insulin being raised when glycosuria appeared and lowered when shock occurred, but in either event by only a small amount. Physiologically minor variations in the amount of insulin greatly alter the percentage figure of the insulin-fat ratio. The regulating dose of insulin was considered to be the amount which most nearly or for the greatest number of days resulted in a balanced state.

For the patients of group 1 who had a carbon dioxide–combining power of plasma greater than 35 volumes per cent the average insulin-fat ratio was 65 per cent, and, excluding patient 3, for those whose alkaline reserve was 35 volumes per cent or less the average insulin-fat ratio was also 65 per cent. The agreement between the ratios for the two groups confirms the impression gained earlier that the degree of acidosis present at the time the patient was admitted to the hospital did not influence the anticipated course of stabilization. It seems evident from the uniformity of the regulating dose of insulin that the deranged carbohydrate-regulating mechanism will accept essentially complete functional relief by exogenous insulin. Such acceptance is in strong contrast to the reaction of this same mechanism during the period of recovery when increasing amounts of endogenous insulin are secreted irrespective of the demand.

Total Units of Insulin Daily.—The amount of insulin administered each day during the period of stabilization is listed. The distribution during the twenty-four hour period is not shown, but, except as noted elsewhere, the apportionment of the total amount conformed closely to the mathematical formula as outlined, although less closely for the earlier than for the later patients.

Urinary Sugar.—Each day's urinary output of sugar is shown below the figure for the amount of insulin administered that day. It would serve no valid purpose to attempt to list the results of the analysis of each of the four partition specimens. A 1 plus qualitative reaction or a trace is considered of no significance and is noted as zero. The most strongly positive reaction obtained in any one day is noted as that day's output of sugar. This method of scoring gives the impression of more significant glycosuria than actually occurred. As an example, the notation of 4 plus, 2 plus, 3 plus for three suc-

cessive days implies much poorer regulation than the actual record of 4 plus, zero, zero, 2 plus; zero, 2 plus, zero, zero; 3 plus, zero, trace, 1 plus. Usually specimens showing a qualitative reaction greater than 2 plus were analyzed quantitatively, in which event the total glycosuria for the day is recorded as grams of sugar excreted. Incomplete partition specimens are recorded only by qualitative notation.

The number of grams of sugar excreted in any one day may give an erroneous picture of the situation. The 5, 11 and 5 Gm. amounts of sugar appearing toward the end of the course of patient 3 were each excreted within the limits of one partition, preceded and followed by periods of complete freedom from glycosuria. No modification was made in the therapeutic program. Within a few days after discharge from the hospital the patient was forced to reduce his intake of insulin to 2 units. A number of the positive reactions shown in the table were caused by the administration of extra carbohydrate for the correction of shock.

Shock.—The incidence of symptoms of shock is not shown in the tables. Early in the development of this regimen shock was considered so favorable an indication of improvement in the condition of the patient that its appearance was welcomed. Later, as the normal rate of improvement emerged as a predictable phenomenon, effort was directed toward keeping to a minimum the clinical manifestations of a too low level of blood sugar or a too rapid fall in the concentration of sugar. One must await the appearance of shock, however, after the initial balance is established, to signal the beginning of the period of recovery. This sign occurs between the sixth and the tenth day after regulation is begun, not six to ten days after it is established. The schedule for the subsequent administration of insulin may permit the entire reduction to be accomplished without the occurrence of more than extremely mild manifestations of shock, which do not necessitate administration of extra carbohydrate.

COMPARISON WITH OTHER METHODS

The minimum data required for proper evaluation of the relative adequacy of different methods of treating juvenile diabetes includes (1) the age of the patient, (2) the duration of the disease, (3) the weight of the patient, (4) the number of calories in the diet, (5) the distribution of dietary carbohydrate, protein and fat, (6) the doses, distribution and type of insulin and (7) the glycemic state as reflected by the level of urinary or of blood sugar or both. Most published observations lack one or more of these categories of essential information.

A small series of patients is presented in table 8, selected from the children with diabetes who were admitted to the Presbyterian Hospital in New York between 1924 and 1930. These patients had had no previous treatment for diabetes, and their records therefore serve as a basis for the evaluation of other methods of therapy.

TABLE 8.—*Results of Treatment of the Initial Attack of Diabetes in Children of Control Series, Treated by a Variety of Methods*

Patient	Age, Yr.	Weight, Kg.	Diet				Period of Hospitalization, Days	Insulin Requirement at Discharge, Units/24 Hr.	Type of Treatment
			Carbohydrate, Gm.	Protein, Gm.	Fat, Gm.	Calories per Kg.			
A	4	18.6	170	50	60	76	82	35	Experimental
B	5	17.7	170	60	70	88	43	24	High caloric diet
C	7	21.5	125	65	75	67	17	30	
D	8	32.3	200	70	100	60	30	38	Ladder type diet
E	9	40.0	125	70	120	47	11	15	Low calories; low carbohydrate
F	12	33.9	200	60	80	52	14	42	Ladder type diet

The records of these few patients illustrate several approved methods of treatment, the ladder type of dietary increase, low calory diet, high fat diet and full diet with adjustment of the intake of insulin to a minimal level. The average daily dose of insulin at the final level was 31 units. The series shows the scattering of end results usually encountered, as judged by the amount of insulin required after stabilization.

The period of hospitalization advised by different clinics varies from ten days or less to three to six months. White [1] stated that an initial period of one to two weeks of hospitalization allows for education and regulation. Jackson [1] stated the belief that a prolonged period of hospitalization is important if optimal conditions are to be established. Usually six to eight weeks is needed to attain stability. Snowden [2] expressed the opinion that because in a patient with previously untreated diabetes the superimposed effect of prolonged high blood

2. Snowden, R. R.: The Importance of Allowing Time for "Physiological Adjustment" in Establishing the Diet in Diabetes, Ann. Int. Med. **14**:789, 1940.

sugar temporarily exaggerates the severity of the diabetes, the time required for physologic adjustment to a suitable regimen cannot be predicted. Nelson [3] stated the belief that the time required for attainment of glycemic equilibrium varies from three or four to ten or twelve weeks and that there are distinct advantages in keeping the child hospitalized for at least the first three or four weeks of the initial period of adjustment. It is universally recognized that after a satisfactory balance is established improvement will occur. Apparently the generally accepted feeling is that after a short period of initial hospitalization further readjustment must be anticipated and carried out at home.

Jackson, Boyd and Smith [4] in 1940 reported a series of observations, extending over three years, for 53 patients, each of whom responded to treatment in a similar manner. Twenty-seven of the patients were selected for study because they were free from complicating factors. For the 27 patients the average dose at the final level, after sixty-seven days of stabilization, was approximately 27 units of insulin. The difference between their figures and the end result for the patients described here may be completely explained by the fact that Jackson, Boyd and Smith applied their method to patients at all stages of the disease. Their report embodies the closest approach to the regimen I have described that I have found in the literature. Although these authors have not differentiated between previously treated and untreated patients, the courses of 10 of their patients, ranging in age from 2 to 11 years, can be compared with my results, since the average duration of symptoms previous to treatment in these 10 patients was one and six-tenths months. The comparison is presented in table 9.

TABLE 9.—*Comparison of Regimen and Results for the Author's Series of Patients with Those for a Series Selected from the Report of Jackson, Boyd and Smith* [4]

	Brush	Jackson, Boyd and Smith
Diet: Carbohydrate-fat ratio	2/1	4/3
Insulin:		
Regulating level, units per day	Averaging ⅔ the number of grams of fat in diet	Determined by trial *
Distribution during 24 hr., % of total dose	53, 13, 27, 7	35, 22, 28, 15
Rate of reduction of insulin	7.5% of regulating dose, followed by set plan below total of 30 units	5% of previous day's dose
Reduction achieved, % of regulating dose	91	68
Duration of course:		
Regulating period	7.2 days	7.8 days
Recovery period	17.0 days	18.5 days
Transition period	0	4.6 days
Stability period	..	28.7 days

* The initial dose of insulin was gaged by the degree of glycosuria, the available dextrose in the diet and the age and height of the child.

In contrast to the experience of Jackson and his associates, no transitional or stabilizing period is encountered in the use of the regimen outlined in this paper. At the end of the period of recovery the patient is free of glycosuria with a low dose of insulin, capable of producing only mild shock. Usually after the patient's discharge from the hospital there is a further reduction of 2 to 4 units below the level of 5 to 8 units with maintenance at this level for months, barring infection or repeated dietary indiscretions.

COMMENT

Similarity of clinical course, amounting virtually to reproducibility of therapeutic results, suggests the operation of physiologic and biochemical laws. Exact formulation of these laws is not possible in the light of current knowledge, but examination of the data permits one to discern certain more or less clearcut trends.

The behavior of our patients indicates that the mechanisms responsible for the regulation of the concentration of blood sugar, disrupted as they are at the time when glycosuria is first recognized in the course of diabetes mellitus, are capable in young patients of a considerable degree of recovery. Since maximal recovery, in terms of the amount of insulin required after stabilization, is achieved only when large amounts of insulin are administered during the periods of regulation and recovery, the beneficial role of therapeutically administered insulin is readily conceived in terms of substitution of the hypodermic injection for the productive effort of an exhausted islet system which, though temporarily incapacitated, can be expected to recover a large fraction of its original competence provided it is not constantly goaded by the driving stimulus of hyperglycemia. Such substitution at a constant level constitutes insulin acceptance by the diabetic child as a probably total replacement mechanism. Teleologic imagery of this sort derives some support from the investigations of others in experimental diabetes.

Allen [5] showed twenty years ago that in a partially depancreatized dog the remaining islet

3. Nelson, W. E.: Personal communication to the author.

4. Jackson, R. L.; Boyd, J. D., and Smith, T. E.: Stabilization of the Diabetic Child, Am. J. Dis. Child. **59**:332 (Feb.) 1940.

5. Allen, F. M.: Experimental Studies in Diabetes; III. The Pathology of Diabetes; I. Hydropic Degeneration of Islands of Langerhans After Partial Pancreatectomy, J. Metab. Research **1**:5, 1922.

tissue was injured by the resulting functional overstimulation; hydropic degeneration of island cells was found in animals within one to three weeks after operation. When the functional strain was relieved, cells in the earlier stages of vacuolation apparently could recover their normal form and granulation, and the pancreatic remnant might subsequently be found to contain the full number of islands of normal size. The majority of cells which reached the stage of extreme vacuolation ordinarily degenerated, despite relief from overstimulation.

Best, Campbell and Haist [6] demonstrated a progressive fall in the amount of insulin in the pancreas to extremely low levels in seven days in dogs rendered hyperglycemic by daily subcutaneous injections of anterior pituitary extract. Experimental diabetes of this type was accompanied with progressive degranulation of the beta cells, followed by hydropic degeneration.[7] On interruption of the injection of hypophysial extract, recovery of the cells and return of the insulin content to normal supervened, provided the pituitary preparation had not been administered over too long a period.

Lukens and Dohan [8] succeeded in producing "permanent" diabetes in cats by removing one half to three quarters of the pancreas and subsequently injecting an anterior pituitary preparation. Animals prepared in this way and observed in the diabetic state for intervals up to eight weeks were subsequently treated with insulin over relatively short periods, nine to thirty-two days, with ensuing clinical and biochemical recovery. Microscopic sections of pancreas examined prior to insulin therapy showed hydropic degeneration of island cells. Subsequent to insulin therapy and during the phase of clinical recovery the remaining pancreatic tissue was morphologically normal. Clinical recovery following treatment with insulin lasted as long as the observations were carried out. The return to the diabetic state of a few of the animals was thought to be explained by superimposed infection, by poor control of the diabetes with insulin or by deferment of treatment with insulin until after the diabetic state had been established for five months or longer; under these conditions atrophy of island tissue was found. Injections of insulin did not of themselves produce atrophy of the islet tissue.

In a few cases of relatively mild as well as early experimental diabetes, recovery was brought about by reduction of the diet, in particular by diminution of the amount of available dextrose offered.[9] Success was obtained also with the use of phlorhizin as a means of preventing hyperglycemia.[10]

All of this evidence is in harmony with the notion that the level of dextrose in the blood is an important factor in the pathogenesis of the permanent diabetic state and that avoidance of hyperglycemia promotes recovery of pancreatic function in the early stages of diabetes. Nothing in the experimental evidence is at variance with the theory that overwork inhibits the recovery of function by the pancreatic islet tissue in the period when recovery is possible.

Logically, then, an ideal therapeutic regimen for children in the early stage of the clinical problem is one which seeks to provide optimal conditions for recovery of the blood sugar-regulating function. Using as a working hypothesis the concept that these favorable conditions can be approximated only if the patient is allowed to suffer no lack of insulin and only when the full requirement of insulin during the period of six to ten days which precedes recovery is furnished by injection, we have shown (1) that significant recovery, in terms of requirement of insulin by injection, is achieved, (2) that the degree of recovery, measured by the same criterion, approaches a limit when other circumstances are favorable and (3) that the rate of recovery for patients presenting a wide variety of clinical manifestations at the time when treatment is begun is so uniform as to suggest that in this respect likewise a limit is being approached or has possibly been reached.

The fact is well recognized that a diabetic child experiencing his first break may suffer a derangement severe enough to cause him to become comatose without incurring irreversible changes in all of the islet tissue (patients 8, 17, 22, 23, 29 and 32). Less familiar but perhaps equally obvious is the fact that during the phase of recovery of the diabetic child under treatment his ability to compensate for hypoglycemia is impaired almost equally with his ability to deal with hyperglycemia. It is as though the convalescent islet tissue were driven to secrete insulin regard-

6. Best, C. H.; Campbell, J., and Haist, R. E.: The Effect of Anterior Pituitary Extracts on the Insulin Content of the Pancreas, J. Physiol. **97**:200, 1939.

7. Ham, A. W., and Haist, R. E.: Histological Effects of Diabetogenic Anterior Pituitary Extracts, Nature, London **144**:835, 1939.

8. Lukens, F. D. W., and Dohan, F. C.: Morphological and Functional Recovery of the Pancreatic Islands in Diabetic Cats Treated with Insulin, Science **92**:222, 1940.

9. Lukens, F. D. W., and Dohan, F. C.: Pituitary-Diabetes in Cat: Recovery Following Insulin or Dietary Treatment, Endocrinology **30**:175, 1942.

10. Lukens, F. D. W., and Dohan, F. C.: Pituitary-Diabetes in the Cat: Recovery Under Phloridzin Treatment, Am. J. Physiol. **133**:368, 1941.

less of the need and in the face of an apparent excess of exogenous insulin and as though the diabetic patient were unable, during this phase of recovery as well as later, to adjust to small increments of exogenous insulin in the same way that the healthy child can. Whether these clinical phenomena are adequately explained solely on the basis of production of insulin is uncertain; possibly other mechanisms come into play.

The results for the 4 patients in group 5 were classed as failures in that the recovery did not conform to the course or attain the goal established for the rest of the series presented. Results for other patients, those of group 2, represent modified failures, the rate of recovery being retarded even though the final insulin requirement was low. Analysis of the records of the patients comprising group 2 suggests that inadequacy in the administration of insulin is their common denominator. Patient 26 remained completely free of glycosuria and of shock for eleven days with a dosage of 33-13-17-0 units of insulin but did not improve until a more effective distribution of the doses (36-8-18-4) was instituted on the twentieth day of the regulatory period. During this time the pancreas was presumably forced to contribute to the insulin needed to maintain apparent stability and was not afforded the proper opportunity to recover, but it is evident that the recognition of such underlying mechanisms presents great practical difficulty with a patient who shows no shock, glycosuria or ketonuria. Other patients whose therapy is open to criticism by my own standards nevertheless followed a favorable course and attained a low eventual requirement of insulin. One patient, no. 25, during fourteen days of erroneous timing of the administration of insulin must have suffered sharp fluctuations in the level of blood sugar, though within narrow limits, calling repeatedly for secretion of endogenous insulin, yet her daily requirements of insulin had dropped below 10 units by the twenty-seventh day of treatment. Her records show a delay of about five days beyond the usual course. Obviously, the question of what constitutes optimal conditions for recovery requires further investigation.

In children the period during which the diabetic state must persist in order to produce permanent functional damage is a variable one. A 9 year old child had been treated with insulin for two weeks nine months prior to admission to the hospital in 1932. The sugar content of the blood was 272 mg. per hundred cubic centimeters, and the carbon dioxide–combining power of the plasma was 22 volumes per cent. Nevertheless, she responded favorably to the administration of large amounts of insulin. Her daily requirement for insulin began to decrease on the ninth day from the maximal level of 58 units, and her final level requirement, 5 units, was reached on the twenty-fifth day. A boy of 10 years with a history of diabetic symptoms for three and one-half months had been treated by regulation of his diet for two months and then with insulin for two weeks. The decrease in his daily requirement for insulin occurred at the expected time, starting from a relatively low initial dose, of 32 units, and ending at the level of 4 units at twenty-eight days. These 2 patients have not been included in the present series.

Most children who have previously been treated with insulin will not recover to the same low level of requirement of insulin as will the previously untreated child. One boy was well launched on his period of recovery when he was taken home, against advice, to seek chiropractic treatment. He returned one month later in coma, and after treatment with what seemed to be maximal doses of insulin his eventual requirement was stabilized at 26 units a day. Such is the usual response of the previously treated child. The golden opportunity for bringing about maximal functional recovery may present itself only once.

The damaging effect of abrupt decrease in the amount of insulin administered because of the occurrence of severe shock, a common signal of beginning recovery, seems to lie in the imposition of an immediate burden on the still ailing blood sugar–regulating mechanism. Similarly, the policy of allowing the patient to eliminate excess sugar himself over a period of days would appear to be comparably harmful.

SUMMARY

Children with diabetes mellitus who have had no previous treatment are capable of recovering an appreciable capacity to regulate the level of blood sugar regardless of the severity of the symptoms when treatment is commenced, provided the therapeutic regimen is directed toward the administration of insulin in such amounts as temporarily to relieve the islet apparatus of any contribution to the total insulin needed by the organism. The characteristic of submitting to the action of large and predictable amounts of exogenous insulin regardless of the apparent clinical severity of the disease has been termed insulin acceptance. The regimen described is based on the hypothesis that the patient's mechanism for regulating the concentration of

blood sugar, deranged in diabetes mellitus, will be restored most nearly to a normal state if insulin is administered to the limit of tolerance. The regimen is applicable to children of all ages and in a wide range of clinical states and provides a practical working guide which by standardizing therapy affords an opportunity for comparing one case with another; under favorable conditions the great majority of patients respond to it with striking uniformity. The patient is given a diet calculated on the basis of his age and weight, not altered according to his appetite; the diet so chosen is held constant during the period of intensive treatment with insulin. After an interval of six to ten days during which the subject's daily requirement of insulin remains fairly constant at a high level, moderate or severe shock marks initiation of the period of functional recovery. From this point on the rate of recovery, as measured by the decrease in the daily requirement of insulin, is so uniform as to be accurately predictable in the majority of instances. After hospitalization for twenty-two to thirty days the child is ready to be cared for at home, free from glycosuria, essentially free from shock and in a stable state on a full maintenance diet controlled by a single daily injection of insulin of between 2 and 8 units.

ERYTHROBLASTOSIS FETALIS

A PROPOSED DEFINITION AND CLARIFICATION OF THE TERM

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In 1912, Rautmann[1] first applied the term *Erythroblastose* to a condition in a hydropic fetus in which there was evidence of excess hemopoiesis in the liver, spleen and kidney. Since that time the term has been used to designate a group of conditions including fetal hydrops, fatal jaundice of the newborn and congenital anemia. Since the discovery of the Rh factor by Landsteiner and Wiener[2] and the application of the knowledge gained through this discovery to the problem of erythroblastosis by Levine and his associates,[3] the term has been employed to designate the condition arising through incompatibility of blood factors between mother and fetus. Confusion now exists in the literature as to what constitutes erythroblastosis. There are those who state that hemolysis is the distinguishing feature of the condition; others state that the essential criterion is the presence in the fetus, at or near term, of extramedullary hemopoiesis, while still others insist that the diagnosis of erythroblastosis should not be made unless the mother's blood is shown to be Rh negative and that of the fetus Rh positive.

How did the man who first used the term define it? Rautmann did not consider that the hemopoiesis was reparatory in nature, compensating for an anemia arising through destruction of erythrocytes, but looked on it as pathologic. The hemosiderin which he found in the liver, but not in the spleen, arose, he thought, through destruction of erythroblasts which contained hemoglobin and not through lysis of mature red cells. On the other hand, those who regard erythroblastosis as synonymous with hemolytic disease of the newborn look on the hemolysis as occurring in the mature red cells. This is evident from the fact that the test for the antibodies causing the hemolysis is made on mature Rh-positive red cells. This assumption is not in line with Rautmann's definition, and either the original definition must be adhered to or, in departing from it, there must be agreement on a uniform interpretation of the term.

It is not easy to adhere to Rautmann's definition because of the inherent difficulty in applying his criteria. It is hard to determine whether iron in the liver of a fetus arose from destroyed nucleated red cells or from mature cells. Inasmuch as the mature cell comes into being through an evolutionary process, begining with a cell without hemoglobin, progressing through megaloblasts, with a little hemoglobin, and normoblasts, with more hemoglobin, to the mature cell, the mere finding of an excess number of megaloblasts or normoblasts in the hemopoietic centers would not necessarily be an indication that it was megaloblasts or normoblasts that had been destroyed. Their presence might indicate that severe anemia brought about by loss of mature cells was evoking a hemopoietic response.

If the term is not to be used as Rautmann defined it, what are to be the criteria for erythroblastosis? Use of the presence of extramedullary hemopoiesis as the criterion, suggested by Potter,[4] encounters the following difficulties: 1. Extramedullary hemopoiesis is the rule in young fetuses, and therefore the diagnosis of the con-

From the Faculty of Medicine, the University of Western Ontario.

Part of the Annual Lecture before the James A. Gibson Anatomical Society, University of Buffalo School of Medicine, Jan. 7, 1944.

1. Rautmann, H.: Ueber Blutbildung bei foetaler allgemeiner Wassersucht, Beitr. z. path. Anat. u. z. allg. Path. **54**:332, 1912.

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dition would be difficult or impossible during the early stages of development (if it is conceded that the disease can be present in the early stages). 2. Since some degree of extramedullary hemopoiesis may persist normally, even up to the time of birth, what is to be the standard by which to judge the amount to be considered above normal, even in fetuses lost late in pregnancy? 3. Inasmuch as extramedullary hemopoiesis can be clearly demonstrated in full term fetuses that do not have hemolytic disease of the newborn, the use of that criterion would lead to confusion, especially if erythroblastosis is considered synonymous with hemolytic disease, as the tendency now seems to be (Levine [3a]).

If hemolysis is used as the criterion (and it must be if the designation suggested by Parsons,[5] Levy [6] and others, "hemolytic disease of the newborn," is accepted) the diagnosis can be made only after the presence of nonhemin iron in the liver has been demonstrated at autopsy. This demonstration is essential to clinch the diagnosis, because in many fetuses and newborn children the blood picture and the histologic structure of the organs are indistinguishable from those in infants with hemolytic disease of the newborn except that there is no evidence of hemolysis when the liver is examined histologically for iron.

In such instances the determination of the Rh factors would not afford conclusive evidence either. Mothers with Rh-negative blood can give birth to normal infants with Rh-positive blood (Koucky [7]); therefore the conclusion that the death of a child with Rh-positive blood born of a mother whose blood is Rh-negative is due to hemolytic disease of the newborn is not warranted until definite proof is obtained that hemolysis occurred. If incompatibility as to the Rh factors between the blood of the mother and that of the fetus is used as the criterion, one will exclude many cases in which the entire picture, clinical and pathologic, is identical with that in cases in which the Rh factor is involved and is in truth hemolytic disease of the newborn, but dependent on blood antigens other than the Rh antigen.

I propose the use of the term erythroblastosis to designate the presence in the circulating blood of the fetus of immature red cells the type or quantity of which is not normal for that period of pregnancy. This would be similar to the use of the term anemia to signify the presence of an amount of hemoglobin less than normal, whatever may be the cause. The following figures were given by Arey [8] for normal percentages of megaloblasts and normoblasts during fetal development. Up to the end of the sixth week the only type of red cell in the blood of the fetus is the megaloblast. By the end of the eighth week normoblasts have appeared and constitute a little more than 50 per cent of the cells. By the tenth week non-nucleated red cells have appeared and make up 25 per cent of the red cells. The normoblasts constitute most of the remaining 75 per cent. By the twelfth week the megaloblasts have all disappeared. When the fetus is 20 weeks old the proportion of nucleated cells (normoblasts) has dropped to 3 per cent, and when it is 24 weeks old, to 1 per cent. From then on these cells form only 0.2 per cent of the total (Wintrobe [9]). With such a disposition of nucleated and non-nucleated forms at various periods of development, one could usually determine whether the nucleated forms were in excess and whether the percentages of megaloblasts were above normal. This criterion would be easy of application at practically all stages of development, early or late, and would be quantitative.

I have drawn up the following scheme to show the conditions under which erythroblastosis might be found and to show their interrelations.

Erythroblastosis

With Iron in Fetal Tissues		Without Iron in Fetal Tissues
Due to		
A. Hemolysis of Megaloblasts of Normoblasts of Mature Red Cells by		B. Factors Other than Hemolysis Operating Early with the site of hemopoiesis Extramedullary and in Bone Marrow
Rh Factor	Other Factors	
Aplastic Phase		Operating Late with the site of hemopoiesis in Bone Marrow
Hemolysis excessive, causes death of fetus before blood can regenerate; iron present, indicating destruction of blood, but no increase in hemopoiesis		Idiopathic Erythroblastosis due to developmental arrest in hemopoiesis, permitting early embryonic type of formation of blood to persist; no destruction, hence no iron

According to this scheme erythroblastosis might be due (A) to hemolysis or (B) to factors other than hemolysis. If the condition is due to hemolysis, the antibodies might conceivably act on the megaloblasts, the normoblasts or the mature cells. Hemolysis might be caused by the Rh complex or by other factors as yet

5. Parsons, L. G.: Hemolysis in Causation of Erythroblastosis Foetalis, Brit. M. J. **2**:675, 1942.

6. Levy, H.: Erythroblastosis Foetalis, Brit. M. J. **2**:738, 1942.

7. Koucky, R. W.: Experiences with the Rh Substance in Transfusion Reactions, Minnesota Med. **26**: 980, 1943.

8. Arey, L. B.: Developmental Anatomy, ed. 4, Philadelphia, W. B. Saunders Company, 1940.

9. Wintrobe, M. M., and Schumacher, H. B.: Erythrocyte Studies in the Mammalian Fetus and Newborn, Am. J. Anat. **58**:313, 1936.

undiscovered. Since hemolysis is the essential feature, iron will be present, especially in the fetal liver. This condition might be termed hemolytic disease of the newborn due to the Rh factor or due to an undetermined factor, or, if the term erythroblastosis is still to be used, it should be called erythroblastosis accompanying hemolytic disease of the newborn.

Erythroblastosis may be caused by factors other than hemolysis, and under these conditions no iron will be demonstrable in the tissues. These factors may operate early or late in development. If they operate early, the stimulus to excess hemopoiesis will continue to exert its effect on the extramedullary centers of hemopoiesis as well as on the bone marrow. If the stimulus arises late in development, after the bone marrow has taken over all the functions of formation of blood, no extramedullary hemopoiesis may be found. Examples of the various types of erythroblastosis without hemolysis will be given shortly.

I have included at the bottom of the scheme of classification two theoretic states. To the left I have placed the term "aplastic phase." It might be possible that the hemolytic factors overwhelmed the fetus, causing its death before there was opportunity for the regeneration of blood. There would probably be iron in the liver, because there would be destruction of blood, but there would be no increase in hemopoiesis. A fetus with such a condition would not show the blood picture of what has been called "erythroblastosis" in the past nor of what I have defined here as "erythroblastosis." However, the condition would be hemolytic disease of the newborn and should be so designated. It would be comparable to the aleukemic phase of leukemia.

The second theoretic state I have designated as "idiopathic erythroblastosis." This condition would be due to developmental arrest in the blood-forming organs, just as there is developmental arrest in other organs when harelip, cleft palate or umbilical hernia persist until birth. A blood picture which is normal in the early embryo would persist through later stages of development, and the fetus would have extramedullary hemopoiesis and immature red cells in the circulating blood but no hemolysis and no iron in the liver.

Three fetuses with the blood picture of erythroblastosis but without hemolytic disease of the newborn will be described briefly. In 2 of these fetuses extramedullary hemopoiesis was present. They would have been considered as having erythroblastosis (and presumably hemolytic disease of the newborn) if extramedullary hemopoiesis were used as the criterion of the disease. In the third fetus the blood picture was one of erythroblastosis, but there was no extramedullary hemopoiesis, for the anoxemia inducing the appearance of immature forms in the circulation came on only a few days before birth, when the liver had relinquished its blood-forming activities.

The first fetus weighed 14½ pounds (6,600 Gm.), showed excess weight of liver and spleen (1,120 Gm. and 20 Gm. respectively), had 21 per cent of the red cells nucleated instead of only 0.2 per cent and showed many areas of hemopoiesis in the liver and spleen, but there was no iron in the liver. The report of the autopsy showed the probable explanation of these conditions. There was advanced stenosis of the ductus arteriosus, resulting in hypertrophy of the heart (a weight of 66 Gm. instead of 18), the wall of the right ventricle was twice the thickness of that of an adult, and the wall of the left ventricle was nearly as thick as that of an adult. The stenosis of the ductus arteriosus forced more blood to flow through the lungs (they weighed 79 Gm. instead of 39) and also caused extreme chronic passive congestion (the liver was fourteen times the normal weight). The stenosis had probably existed from the time at which the sixth aortic arch developed; therefore the anoxemia and the resultant excess hemopoiesis had existed throughout development.

The second fetus may have had idiopathic erythroblastosis, since there were no autopsy observations to explain the presence of immature cells in the circulation or of large numbers of hemopoietic areas in the liver and spleen. The fetus was full term, weighed 11 pounds (5,000 Gm.) had many nucleated red cells and immature white cells in the blood and had an enlarged liver (321 Gm.). The liver contained no iron, and therefore the condition was not hemolytic disease of the newborn. There was no syphilis. The mother had eight pregnancies, four of which terminated in miscarriages or stillbirths.

The third fetus exhibited the blood picture of erythroblastosis, with many nucleated red cells and few mature white cells, but there was no extramedullary hemopoiesis and there was no iron in the liver. The parents both had Rh-positive blood. The explanation of the blood picture was probably anoxemia in the fetus during the last three or four days before birth. A recent retroplacental hemorrhage was evident when the placenta was delivered. The pulse of the fetus had fallen to 90 the day of birth; asphyxia had deepened; amniotic fluid had been aspirated and filled the trachea and bronchi, and meconium had been discharged into the amniotic fluid. Although the making of a routine smear of blood from the cord is an excellent procedure in the attempt to recognize hemolytic disease of the newborn immediately, it must be remembered that not all infants who show a blood picture similar to that seen in hemolytic disease have the disease. This fetus is an example.

One of the confusing problems of hemolytic disease of the newborn is that antibodies cannot always be demonstrated in the mother's serum either before or at the time of birth of a fetus which obviously shows all the signs of the disease, even to the presence of iron in the liver. How can the blood of the mother destroy blood

cells in the fetus with antibodies that cannot be demonstrated?

The following line of argument is theoretic, but it explains some of the obscure points in connection with this condition. Suppose that the antigen develops in the early stages of the formation of red blood cells but that it is not chemically identical with the mature antigen. It may have two or perhaps three forms, corresponding with the megaloblast, the normoblast and the mature red cell stage of development. The cells which escape from the fetal villi into the maternal circulation may be megaloblasts, normoblasts or, later, mature red cells. The antibodies which develop in the mother will correspond with and be specific for the antigens which produced them. These antibodies return to the fetal circulation and destroy the cells for which they are specific. Because all three forms have iron in them, iron can be demonstrated in the fetal liver in each instance. The fetus responds by increasing the output of the type of cells which was destroyed. If it is megaloblasts which were destroyed, this type of cell is caught up in the circle of destruction and formation; hence the fetus will have the megaloblast for the most part in its hemopoietic areas and as the predominant type of nucleated red cell in the circulation. Similarly, when it is normoblasts which are destroyed the predominant type of nucleated cell will be the normoblast. If the blood of the mother is examined for antibodies, during the pregnancy, it may show none, because it is tested against mature antigens, by the use of mature Rh-positive red cells. The mother may, however, have antibodies against Rh-positive megaloblasts or normoblasts, and despite the negative reactions for antibodies she may give birth to a fetus showing destruction of blood due to antigen-antibody reactions. Had her blood been tested with Rh-positive megaloblasts or normoblasts, the antibodies might have been demonstrable. Since hydropic fetuses have excess megaloblasts it may be that the cells which escaped into the maternal circulation were megaloblasts. In instances in which antibodies are demonstrable in the mother it may be that mature cells escaped, during later development, as well as megaloblasts. Hydrops may develop in the fetus when the escaping cells are megaloblasts, fatal icterus when the escaping cells are normoblasts and congenital anemia when the escaping cells are all of the mature type. However, there may be only two stages of maturity of the Rh factor.

Such a line of reasoning explains several things, although it leaves others still to be elucidated. It would explain the three grades of severity of the disease. It would explain also the excess of megaloblasts in hydrops, the preponderance of normoblasts in icterus and the lack of mature erythrocytes in congenital anemia and also the lack of demonstrable antibodies in some instances. It might explain the edema in hydrops; the capillaries of the fetus may become plugged with large megaloblasts, permitting stasis and seepage of fluid into the tissues. It does not, so far as I can see, offer an explanation of the death of infants with fatal icterus within a day or so after birth.

Another explanation for failure in the demonstration of agglutinins in the serum of a mother who is carrying a fetus with hemolytic disease is furnished by recent research [10] which indicates that there are at least six different Rh factors (others will doubtless be found in time) which act as antigens. Two of these, Rh_1 and Rh_2, are common and were the first to be found. The remaining four are relatively rare. The failure to demonstrate the presence of antibodies when the mother's serum is tested with preparations of only the commoner types of Rh-positive antigens may depend on the fact that the Rh factor against which the mother is immunized is one of the uncommon ones. Testing the serum of the mother against the blood cells of the father of the fetus should reveal these antibodies if this is the explanation of the failure to demonstrate them. Should the mother's serum still show no antibodies, the explanation given earlier in this paper may be the correct one, namely, that the fetal antigens may differ from the mature antigens and that the antibodies manufactured by the mother were against the fetal type of antigens.

SUMMARY

Erythroblastosis is defined as a condition in which the blood of the fetus exhibits immature cells of the erythrocytic series which are not normal, either as to type or as to quantity, for the stage of development of the fetus.

This condition may be elicited by numerous factors, may or may not be accompanied with hemolysis and may or may not be accompanied with extramedullary hemopoiesis. It includes hemolytic disease of the newborn as well as erythroblastosis due to factors other than hemolysis. When it is due to an antigen-antibody

10. (*a*) Race, R. R.; Taylor, G. L.; Boorman, K. E., and Dodd, B. E.: Recognition of Rh Genotypes in Man, Nature, London **152**:563, 1943. (*b*) Race, R. R.; Taylor, G. L.; Cappell, D. F., and MacFarlane, M. N.: Recognition of a Further Common Rh Genotype in Man, ibid. **153**:52, 1944.

reaction there will be hemolysis, with accumulation of iron in the fetal liver, and there will usually be persistent extramedullary hemopoiesis. This form of erythroblastosis is hemolytic disease of the newborn. In the majority of instances the hemolysis appears to be due to the Rh factor complex.

Factors such as anoxemia cause erythroblastosis, as here defined, but not hemolysis. If they begin to operate early in development, extramedullary hemopoiesis will persist; if they begin just before term, formation of blood may be restricted to the bone marrow.

A tentative explanation of the failure to find antibodies in the blood of the mothers of some fetuses showing erythroblastosis is advanced, based on a supposed immaturity of the antigen as it exists in the immature red cell, with a corresponding specificity of the antibody for this particular antigen. At present the demonstration of the antibody depends on its reaction with the antigen as it exists in the mature red cell. Testing of the blood of the mother with that of the fetus may demonstrate the presence of such antibodies. Another possible explanation is based on the recently discovered fact that there are at least six different Rh factors. Preparations of only the two commoner types of antigen are employed in the usual tests.

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ORAL MONILIASIS IN NEWBORN INFANTS

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Oral moniliasis occurs frequently in newborn infants and probably is exceeded only by impetigo neonatorum in its incidence in nurseries for newborn infants. This study was undertaken to investigate further some of the factors which may be related to the incidence, the source and the spread of oral moniliasis in newborn infants.

Oral swabs were obtained from apparently normal newborn infants in order to investigate the frequency with which they contained Monilia and to study oral moniliasis preclinically, if perchance thrush developed later in any of the infants. Vaginal swabs were obtained from the mothers of some of these infants during labor and/or at delivery in order to determine the relationship between maternal vaginal and infantile oral moniliasis. Whenever thrush of the mouth became clinically manifest in infants not in the group being studied, laboratory confirmation of the diagnosis was attempted by culturing oral swabs for Monilia (Candida) albicans.

On two occasions oral swabs were obtained from the personnel in the nursery in order to determine whether there was a carrier of M. albicans. The possible role of air-borne infection was considered, and culture plates which had been exposed at strategic points in the nursery were studied mycologically. Nipples used by infants with clinical thrush, as well as other appropriate objects in the nursery, were tested culturally for M. albicans. Furthermore, nipples were experimentally contaminated, immersed in boiling water for various periods and then tested for sterility. The resistance of M. albicans to drying was determined under experimental conditions.

A small number of the infants who had had thrush were examined periodically, after they were discharged from the hospital, for the persistence of clinical manifestations of the infection, for the continued presence of M. albicans in the mouth and for the development of antibodies.

MATERIALS AND METHODS

Clinical Materials and Methods.—The presence of Monilia in the mouths of newborn infants was determined by culturing oral swabs. In each instance a dry cotton applicator was rolled gently over the tongue, over the buccal mucosa of one cheek, over the palate and finally over the buccal mucosa of the other cheek while the mouth of the infant was held open by depressing the chin with the left thumb and immobilizing the mandible with the fingers of the left hand. Six specimens were obtained from each infant as follows: no. 1, during the interval between birth and the initial feeding, at 12 hours of age; no. 2, during the interval between the initial prelacteal feeding and the first breast feeding, at 24 hours of age; no. 3, on the second or third day of life; no. 4, on the third or fourth day of life; no. 5, on the sixth or seventh day of life, and no. 6, on the ninth or tenth day of life. The clinical appearance of the mouth was recorded each time a specimen was collected. Data are available for 107 infants studied in this manner. During the period of observation 34 infants in an adjacent nursery had clinical thrush, the diagnosis of which was confirmed in the laboratory by culturing of a single oral swab.

Vaginal swabs obtained from the mothers of some of these infants were also cultured for Monilia. The specimens were collected on dry cotton applicators, which were then immersed in 0.5 cc. of veal infusion broth and stored in the refrigerator until they could be delivered to the laboratory, within the next twelve hours. The specimens were obtained at the time of the initial care of the patient or immediately before the delivery of the infant. In a few instances two specimens were obtained from the same mother. Data are available for 57 mothers studied in this manner.

Mycologic Methods.—Dry cotton applicators were found to be satisfactory for the collection of specimens in the daytime, during laboratory hours, since most specimens were cultured within thirty minutes from the time of collection. In order to prevent the drying out of material obtained during the night we employed a special apparatus which consisted of a 120 by 16 mm. cotton-plugged test tube in which was placed a 50 by 8 mm. open tube containing 0.5 cc. of veal infusion broth. For sterilization the cotton applicator was placed within the larger tube and outside of the smaller one, but immediately after the specimen had been obtained the applicator was immersed in the small tube of broth. Specimens collected in this manner remained in the refrigerator or at room temperature until delivered to the laboratory.

The technic of Martin, Jones, Yao and Lee[1] for the isolation and identification of Monilia was employed. Another step was added by inoculating a veal infusion-blood agar plate with each swab before it was streaked on Sabouraud's agar. The purpose of this additional blood agar culture was to obtain information concerning the bacteriologic flora of the infants' mouths and of the mothers' vaginal tracts. Both agar plates were examined for the presence of yeastlike colonies, after

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1. Martin, D. S.; Jones, C. P.; Yao, K. F., and Lee, L. E., Jr.: Practical Classification of Monilias, J. Bact. **34**:99-129 (July) 1937.

they had been incubated overnight at 37 C. If one or more such colonies appeared in either plate, the culture was considered to be positive for Monilia and was reported to the clinician as such immediately. Although the initial appearance of monilial colonies was rarely delayed beyond the second day, all cultures were examined daily for ten days before they were discarded.

The technic of Martin and his co-workers proved to be satisfactory except for the use of the corn meal[2] slide culture to demonstrate the production of myceliums and chlamydospores by M. albicans. Although the details of the method were strictly followed, many strains produced scant myceliums with few chlamydospores; a few strains, otherwise typical of M. albicans, were still without any chlamydospores after several trials with duplicate preparations. In these few instances an identification of M. albicans was made in spite of the absence of chlamydospores and, occasionally, in spite of the failure to demonstrate the characteristic "treelike" mycelial branching.

fed. All of the infants received, after the milk, 5 per cent dextrose in water to which 0.25 per cent of sodium chloride had been added.

In every instance in which the presence of M. albicans in the oral swab was demonstrated culturally, clinical thrush of the mouth developed in the infant within two to nine days. In table 3 are listed the patients with clinical thrush, arranged chronologically, with the interval between birth and the time at which Monilia was first obtained and the interval which elapsed before the disease became manifest clinically. The grouping facilitates the identification of the "epidemic" cases. The infants from whose mothers

TABLE 1.—*Frequency Distribution of Infants Studied by Weight, Sex and Race*

Weight at Birth	White			Negro			Total		Grand Total
	Male	Female	Total	Male	Female	Total	Male	Female	
5 lb to 5 lb. 7 oz. (2,268 to 2,494 Gm.)	..	1	1	..	..	..	..	1	1
5 lb. 8 oz. to 5 lb. 15 oz. (2,495 to 2,721 Gm.)	3	2	5	..	1	1	3	3	6
6 lb. to 6 lb. 7 oz. (2,722 to 2,948 Gm.)	1	3	4	1	2	3	2	5	7
6 lb. 8 oz. to 6 lb. 15 oz. (2,949 to 3,174 Gm.)	6	11	17	3	..	3	9	11	20
7 lb. to 7 lb. 7 oz. (3,175 to 3,401 Gm.)	15	14	29	1	..	1	16	14	30
7 lb. 8 oz. to 7 lb. 15 oz. (3,402 to 3,628 Gm.)	11	7	18	..	1	1	11	8	19
8 lb. to 8 lb. 7 oz. (3,629 to 3,855 Gm.)	10	4	14	..	..	..	10	4	14
8 lb. 8 oz. to 8 lb. 15 oz. (3,856 to 4,081 Gm.)	2	2	4	..	..	..	2	2	4
9 lb. to 9 lb. 7 oz. (4,082 to 4,308 Gm.)	4	..	4	1	..	1	5	..	5
9 lb. 8 oz. to 9 lb. 15 oz. (4,309 to 4,534 Gm.)	1	..	1	..	..	..	1	..	1
Total	53	44	97	6	4	10	59	48	107

TABLE 2.—*Frequency Distribution of Clinical Cases of Thrush by Weight, Sex and Race of the Infants*

Weight at Birth	White			Negro			Total		Grand Total
	Male	Female	Total	Male	Female	Total	Male	Female	
5 lb. to 5 lb. 7 oz. (2,268 to 2,494 Gm.)	..	..	..	..	..	..	..	..	..
5 lb. 8 oz. to 5 lb. 15 oz. (2,495 to 2,721 Gm.)	1	1	2	..	..	..	1	1	2
6 lb. to 6 lb. 7 oz. (2,722 to 2,948 Gm.)	..	..	..	..	..	..	..	..	..
6 lb. 8 oz. to 6 lb. 15 oz. (2,949 to 3,174 Gm.)	3	1	4	1	..	1	4	1	5
7 lb. to 7 lb. 7 oz. (3,175 to 3,401 Gm.)	5	2	7	..	..	..	5	2	7
7 lb. 8 oz. to 7 lb. 15 oz. (3,402 to 3,628 Gm.)	1	1	2	..	..	..	1	1	2
8 lb. to 8 lb. 7 oz. (3,629 to 3,855 Gm.)	2	1	3	..	..	..	2	1	3
8 lb. 8 oz. to 8 lb. 15 oz. (3,856 to 4,081 Gm.)	..	..	..	..	..	..	..	..	..
9 lb. to 9 lb. 7 oz. (4,082 to 4,308 Gm.)	1	..	1	..	..	..	1	..	1
9 lb. 8 oz. to 9 lb. 15 oz. (4,309 to 4,534 Gm.)	..	..	..	..	..	..	..	..	..
Total	13	6	19	1	..	1	14	6	20

RESULTS

Relation of Clinical Thrush to the Presence of M. Albicans.—The distribution of the 107 infants according to weight, sex and race is shown in table 1. Yeast forms culturally identified as M. albicans were found in 20 of the infants, 18.7 per cent. The distribution of the infants who had oral moniliasis according to weight, sex and race is shown in table 2. Fifteen of the infants were breast fed; the remaining 5 received breast milk supplemented with an evaporated milk formula. Of the whole group of 107 infants, 80 were breast fed, 24 received breast milk and evaporated milk and 3 were entirely artificially vaginal swabs were obtained are especially designated. The average interval after birth before cultural evidence of the presence of Monilia was obtained was four and eighty-five hundredths days. The average interval between the time the first positive culture was obtained and the onset of clinical thrush was three and thirty-five hundredths days. The average interval after birth for the development of clinical thrush was eight and two-tenths days.

In addition to 20 infants in the group studied, 34 others had clinical thrush during the course of the investigation. Since M. albicans was demonstrated in an oral swab from every one of these infants, there was perfect correlation between the clinical diagnosis of oral moniliasis and the isolation of M. albicans from the mouth for a total of 54 patients. Furthermore, thrush was not diag-

2. Quaker Oats Co. yellow corn meal was used.

TABLE 3.—*Development of Clinical Thrush in Relation to Positive Infantile Oral and Maternal Vaginal Cultures*

Patient	Date of Birth	Positive Culture for M. Albicans: Date	Positive Culture for M. Albicans: Specimen, No.	Interval After Birth, Days	Clinical Thrush, Date	Interval After Positive Culture, Days
J. H.	12/25/41	12/27/41	3	2	1/ 3/42	7
J. S.	1/ 1/42	1/ 5/42	4	4	1/10/42	5
D. B.	12/28/41	1/ 6/42	6	9	1/ 9/42	3
C. F.	12/30/41	1/ 6/42	5	7	1/ 9/42	3
J. D.	12/30/41	1/ 6/42	5	7	1/ 9/42	3
H. T.	1/ 1/42	1/ 7/42	5	6	1/10/42	3
A. P.†	1/ 5/42	1/ 8/42	4	3	1/11/42	3
R. K.	1/14/42	1/20/42	5	6	1/23/42	3
B. K.	1/15/42	1/21/42	5	6	1/24/42	3
V. D.†	2/ 2/42	2/ 2/42	2	1	2/11/42	9
M. W.†	3/18/42	3/24/42	5	6	3/26/42	2
D. C.*	3/26/42	4/ 1/42	5	6	4/ 2/42	1
R. G.*	4/12/42	4/12/42	1	1	4/15/42	3
J. M.†	4/ 9/42	4/13/42	4	4	4/16/42	3
T. C.†	5/ 3/42	5/ 3/42	2	1	5/ 8/42	5
A. M.†	5/ 5/42	5/ 5/42	2	1	5/ 8/42	3
J. H.†	5/ 9/42	5/12/42	4	3	5/15/42	3
M. L.*	5/ 8/42	5/14/42	5	6	5/16/42	2
E. D.*	5/ 9/42	5/18/42	6	9	5/21/42	3
G. L.*	5/10/42	5/19/42	6	9	5/19/42	..

† Vaginal swab of mother of infant contained M. albicans.
* Vaginal swab of mother of infant did not contain M. albicans.
Vaginal swabs were not obtained from the mothers not specially designated.

extensive but is likewise limited to the dorsum of the tongue. The plaques which adhere to the tongue and to other portions of the mucous membrane of the mouth in oral thrush are difficult to remove, and when removed they leave denuded areas. In table 4 are summarized the relationships between the clinical findings and the results of the oral cultures for the entire series of subjects. The clinical examinations were made at the same time as the cultures.

Sources of Infection.—Vaginal Tract of the Mother at Delivery: Vaginal swabs were obtained from 57 of the mothers during labor and/or at delivery. The results of the cultural studies of the swabs are correlated with those of studies of the infants' mouths in table 5. The occurrence of oral thrush in 6 of 13 infants whose mothers had M. albicans in the vaginal flora is significant when compared with the incidence of oral thrush in only 4 of 38 infants from whose mothers' vaginal swabs Monilia was not isolated and in only 5 of the 44 infants from whose mothers either no species of Monilia was

TABLE 4.—*Clinical Symptoms in Infants Studied*

Report of Oral Culture	Number of Infants	Clinical Symptoms	Clinical Examinations at Which Symptom Was Observed, No.: 1	2	3	4	5	6	All
No yeast	83	Fur *	6	5	10	19	31	25	..
		Coat †	..	1	2	8	11	15	..
		None	..	..	..	..	..	..	28
		Fur	..	..	..	..	..	..	5
Unclassified forms of yeast	3	Fur	..	..	..	1	..	1	..
		Coat	..	..	..	..	1	..	..
		None	..	..	..	..	..	..	2
		Culture positive for first time	..	..	..	..	1	2	..
M. stellatoidea	1	Fur	1	1	1	1	..	..	..
		Coat	..	..	..	..	1	1	..
		Culture positive for first time	..	..	..	1	..	..	..
M. albicans	20	Fur	2	1	1	5	3	..	..
		Coat	..	1	3	3	8	2	..
		None	..	..	..	..	..	..	1
		Thrush ‡	..	..	..	..	4	13	..
		Culture positive for first time	1	3	1	4	8	3	..
	107								

* Fur indicates a uniform white covering on the dorsum of the tongue.
† Coat indicates a heavier uniform covering on the dorsum of the tongue.
‡ In 3 other cases thrush was diagnosed clinically later.

nosed clinically in any infant from whom only yeast forms other than M. albicans, namely, Monilia stellatoidea and Martin's unclassified form, were isolated. Furring of the tongue and coating of the tongue were seen in many patients in whom thrush did not develop, and they were not interpreted as precursors of clinical thrush. Moreover, there was no correlation between furring or coating of the tongue and the presence of pneumococci, hemolytic streptococci or staphylococci in the mouth. "Furring of the tongue" denotes the existence of a thin uniform covering on the dorsum of the tongue; in coating of the tongue the covering is relatively more

TABLE 5.—*Comparison of Mycologic Reports for Mother and for Infant*

Vaginal Swabs, Mothers		Oral Swabs, Infants		
M. albicans	13	No yeast	7	
		M. albicans	6	(2 in second specimen) (3 in fourth specimen) (1 in fifth specimen)
M. candida	3	No yeast	3	
M. stellatoidea	3	Negative	1	
		M. stellatoidea	1	(in fourth specimen)
		M. albicans	1	(in sixth specimen)
No yeast	38	Negative	33	
		Unclassified yeast	1	(in fifth specimen)
		M. albicans	4	(2 in fifth specimen) (1 in sixth specimen) (1 in all specimens)

obtained or only forms other than M. albicans (table 6).

In table 7 the age at which thrush became manifest culturally is shown for the infants whose mothers had vaginal moniliasis and for those whose mothers were free of this infection. For the infants whose mothers harbored M. albicans the mean time of onset was three days after birth; for the infants whose mothers did not have M. albicans it was six and two-tenths days.

TABLE 6.—*Incidence of Oral Moniliasis in Infants According to Mother's Vaginal Flora*

Mother's Vaginal Swab	Infants: Oral Moniliasis	Infants: No Oral Moniliasis	Total
M. albicans	6	7	13
No Monilia	4	34	38
Total	10	41	51
$\chi^2 = 7.8$; P is between 0.01 and 0.001			
M. albicans	6	7	13
Other forms of Monilia or no Monilia	5	39	44
Total	11	46	57
$\chi^2 = 7.8$; P is between 0.01 and 0.001			

A value for "P" of 0.05 or less is commonly accepted as indicating a significant difference. In this instance the value of "P" is between 0.01 and 0.001, which indicates that a difference as large as or larger than that observed might arise by chance alone in less than 1 per cent of similar trials.

TABLE 7.—*Occurrence of Oral Thrush in Infants in Relation to Vaginal Moniliasis in Mothers*

Vaginal Swabs from Mother	Infant	Date of Birth	Oral Swabs Positive for M. Albicans, Date	Interval, Days	Average Interval, Days
Positive for M. albicans	A. P.	1/ 5/42	1/ 8/42	3	3
	M. W.	3/18/42	3/24/42	6	
	J. M.	4/ 9/42	4/13/42	4	
	T. C.	5/ 3/42	5/ 3/42	1	
	A. M.	5/ 5/42	5/ 5/42	1	
	J. H.	5/ 9/42	5/12/42	3	
Negative for M. albicans	D. C.	3/26/42	4/ 1/42	6	6.2
	R. G.	4/12/42	4/12/42	1	
	M. L.	5/ 8/42	5/14/42	6	
	E. D.	5/ 9/42	5/18/42	9	
Positive for M. stellatoidea	G. L.	5/10/42	5/19/42	9	

One infant (A. P.) had only one postpartum contact with his mother, who had vaginal moniliasis, and thereafter he was fed breast milk from a bottle in the nursery. It is possible that oral thrush in this instance may have been acquired by contact in the nursery, since other infants with the disease were present in the nursery at the same time (table 3). There were 2 instances (cases of V. D. and M. W.) in which the only infection with Monilia at a specific time developed in an infant whose mother had M. albicans in the vagina. One infant (V. D.), whose mother was reported to have been treated for vaginal mycosis during pregnancy but from whom, unfortunately, no vaginal swab was obtained at the time of delivery, had M. albicans in the second specimen and in each one thereafter; oral thrush developed nine days after the organism was first found, at a time when there was no other infant with thrush in the nursery. There was no other infant with thrush in the nursery at the time another infant (D. C.), whose mother's vaginal swab was negative for M. albicans, acquired the disease. An infant (R. G.) whose mother's vagina did not contain Monilia showed M. albicans in the first oral specimen, obtained when the child was twelve hours of age, at a time when M. albicans was demonstrated in an oral swab from a 3 day old infant (J. M.) whose mother had monilial vaginitis. A close relationship to maternal moniliasis is suggested in 2 instances in which M. albicans was present in the mouth of an infant (T. C. and A. M.) twelve hours after birth, at a time when there was no other infant with thrush in the nursery. There was one episode in which the first infant to show signs of oral moniliasis (J. H.) was born of a mother who had vaginal moniliasis and in which other infants (M. L., E. D. and G. L.), whose mothers did not have moniliasis, acquired thrush.

There was 1 instance in which M. stellatoidea was obtained from a mother's vagina and from her infant's mouth from the third day on without the development of clinical symptoms of oral thrush. In another instance in which the mother's vaginal swab showed M. stellatoidea oral thrush developed in the infant on the ninth day of life, associated with the presence of M. albicans in the infant's mouth and at a time when other infants in the nursery had thrush. There were no oral lesions in the third infant whose mother's vaginal swab showed M. stellatoidea or in the infants whose mothers had M. candida in the vaginal discharge.

Nursery Personnel: Twice during outbreaks of thrush in the infants oral cultures were made for the nursery personnel, by the same technic as already described. Of the 17 persons who were examined, 10 were included on both occasions. None of the cultures was positive for M. Albicans.

Nursery Air: On twenty occasions during a period of fifty-six days Sabouraud's dextrose agar plates were exposed to the air at selected locations in the nursery. Each test consisted of the exposure of eight to ten plates for periods varying from thirty minutes to two hours. The locations for the exposures included window sills, tops of tables, crib blankets and low and high spots near doors. In order to include

periods of activity and periods of relative quiet in the nursery, the time at which the plates were exposed varied from early morning to late afternoon. A total of 168 plates so exposed were incubated for five to six days and examined for M. albicans. Although 30 per cent of the plates contained yeastlike colonies, none of the organisms proved to be M. albicans. In fact, the number of yeastlike colonies on any one plate seldom exceeded two or three, which suggested that the nursery air was not heavily contaminated with yeastlike fungi during the period of this study. The predominating fungus recovered from the air belonged to Martin's unclassified form of Monilia. It is pertinent to mention that an organism which appeared to be identical with this one was isolated on three occasions from the mouths of infants who were free of thrush.

The method employed in the survey of the air was admittedly crude, and it is possible that the failure to isolate M. albicans was due to the use of an inadequate technic. Nevertheless, since 30 per cent of the exposed plates contained yeastlike fungi and since most of these fungi were species of Monilia, we feel justified in concluding that transmission in air was not the principal mode of infection of infants with oral moniliasis.

Fomites: On several occasions cultures were made from rubber nipples and from bottles which had been used by infants with thrush, as well as from a solution of sodium bicarbonate in which the used nipples were immersed and from the surfaces of the tables which held these materials. All of these cultures contained M. albicans. Therefore it seemed desirable to test the ability of this organism to withstand drying and to survive exposure to boiling water.

An eighteen hour culture in Sabouraud broth containing only yeasts was used to contaminate several pieces of sterile filter paper, 1 cm. square. Each piece of paper was then permitted to dry in a small sterile test tube containing a few glass beads. At weekly intervals one of the squares of paper was placed in a tube of Sabouraud broth to determine the viability of the test organism. Until the end of the second week the tests revealed M. albicans; subsequently the results were negative. M. albicans produces chlamydospores, the resistance of which is much greater than that of the vegetative form of the organism. Chlamydospores, however, do not develop under the conditions existing in the mouth, so that a study of the resistance of chlamydospores did not seem to be indicated.

A six day culture of M. albicans on corn meal agar (chlamydospores present) was removed to a large test tube containing distilled water. Adherent pieces of agar and the fungous growth were broken up by maceration and by the use of a glass rod. After light centrifugation the resulting suspension had a turbidity of approximately 3.0 by the McFarland scale. Into this suspension were dipped several dry, sterile rubber nipples; on removal these were allowed to dry in the air for two hours, in an upright position on a sterile towel. Each nipple was then placed, by means of flamed forceps, in a wide-mouthed gauze-stoppered bottle containing 30 cc. of distilled water, which for at least five minutes previously had been maintained at 98 to 99 C. (inside temperature) in a boiling water bath. At the end of the desired period each bottle was quickly removed to cold water, and 3 cc. of ten times concentrated Sabouraud broth was added. Duplicate bottles were tested for each interval. After incubation for five days at 37 C. cultures showing evidence of growth were subcultured and the organisms identified. The results indicated that nipples contaminated in the manner described were freed of living M. albicans by immersion in boiling water for approximately five minutes. All tests using intervals shorter than five minutes showed the organism to be present, and all tests using longer intervals failed to reveal it.

Follow-up Studies.—Some of the infants who had had oral moniliasis were found to harbor the yeast after the clinical disease had disappeared. Oral swabs from 12 infants who had had thrush of the mouth were obtained at one to three subsequent visits to the clinic during a period of three to twelve weeks after the onset of the disease. Of 9 infants who had oral cultures positive for M. albicans for as long as twelve weeks after the onset of the disease 8 were asymptomatic; the ninth infant still had clinical thrush of the mouth nine weeks after he was discharged from the hospital. Unfortunately, it is not known whether the mother of this infant was infected.

Samples of blood were collected from 7 infants six weeks to three months after the onset of the oral moniliasis. The serums were tested for agglutinins of M. albicans. Because of the spontaneous clumping of yeast cells, the use of agglutination tests was discontinued without obtaining evidence of the presence of a specific antibody. The same serums were then tested against monilial extracts by the precipitin method of Lamb and Lamb.[3] Four of the serums caused a small amount of precipitation, but the results were inconclusive, and no further attempt was made to demonstrate the presence of specific antibody in convalescent serum.

COMMENT

The possibility that M. albicans is transmitted from the mother's vaginal tract to the infant's mouth has been considered by others in previous investigations.[4] Ludlam and Henderson[5] ex-

3. Lamb, J. H., and Lamb, M. L.: Grouping of Monilias by Fermentation and Precipitin Reactions, J. Infect. Dis. **56**:8-20 (Jan.-Feb.) 1935.

4. (*a*) Haussmann, D., cited by Hesseltine and others,[4g] Bland and others,[4h] Woodruff and Hesseltine[4i] and Ludlam and Henderson.[5] (*b*) Veit, cited by Hesseltine and others.[4g] (*c*) Noack, F., cited by Hesseltine

(Footnote continued on next page)

pressed the opinion that there is no significant relationship between vaginal infection of the mother and oral infection of the infant, although M. albicans is not uncommonly found in the mother's vagina. They stated the belief that the mother is more likely to be a "medium of infection" than the source.

Hesseltine, Borts and Plass [4g] injected monilias cultured from material from the vaginas of patients with moniliasis directly into the buccal cavities of healthy newborn infants less than one week of age and produced clinical thrush in 9 of 24 instances and then recovered the fungus and identified it as identical with that injected originally. Bland, Rakoff and Pincus [4h] inoculated monilias obtained from a patient with oral thrush into vaginal mucosa and produced vaginal moniliasis in 7 of 12 instances. In this experimental study of vaginal and cutaneous moniliasis the incubation period averaged thirty-nine hours and ranged from twenty-four to ninety-six hours.

Faber and Clark [4e] recommended isolation of an infant whose mother has vaginal thrush. Hesseltine [6] recommended a single prophylactic application of 1 per cent aqueous solution of gentian violet immediately after birth to the oral cavity of any infant whose mother has vaginal mycosis.

In our study the interval between the birth of the infant and the cultural demonstration of the presence of M. albicans in the infant's mouth averaged three days in those instances in which the mother had vaginal mycosis in contrast to six and two-tenths days when the mother's vaginal swab failed to show Monilia. Since the incubation period for experimentally produced moniliasis averaged thirty-nine hours,[4h] it seems that factors other than contact at birth may have a causal relationship in the development of thrush of the mouth. The possibility that the disease occurs after repeated postpartum contacts with the infected mother must be considered. In these instances the infection may occur otherwise than directly from the vagina; the mother's skin or clothing may be contaminated with the fungus, and therefrom the oral inoculation of the infant may be made.

Contact in the nursery may cause secondary cases of oral moniliasis. It is also possible that air currents constitute a means of transmission. In this study, however, M. albicans was not isolated from any of the plates which had been exposed at strategic points for air currents in the nursery where there had been infants with oral thrush. Fungoid organisms were present in these cultures, but none of them proved to be M. albicans.

Preceding illness in the infant did not seem to be an important factor in relation to the development of oral thrush. Whether the development of thrush is related to persistent vomiting or to the presence of milk in the mouth could not be ascertained. There were 3 infants, however, in whom vomiting preceded the development of thrush. Unfortunately, the mothers of these infants had not been studied for vaginal mycosis. There were no instances of other significant morbidity in the infants in this series. Thrush of the mouth did not develop concurrently in any of the premature infants, who were attended by a separate nursing staff in a nursery adjacent to the one for full term infants who had been exposed to thrush. Whether local trauma was a factor could not be satisfactorily evaluated. It is of interest to note that the incidence of the disease did not seem to be increased by the procedures used in taking the oral specimens from the infants. In fact, during the period of observation thrush of the mouth was actually more prevalent in an adjacent nursery than in the one in which the routine study was conducted. It should be stressed that extremely gentle rolling of the swab was always employed in taking these specimens in order not to cause local trauma. In subsequent examinations of the mouths of the infants studied there was no clinical evidence of injury to the mucosa. Only two persons participated in the clinical portion of this study, so the technic can be considered to have been uniform.

The investigation of oral moniliasis in newborn infants was carried out by a small group of persons who regularly performed the same tasks. Such a plan has distinct advantages over

and others.[4g] (*d*) Cron, R. S., cited by Hesseltine and others,[4g] Bland and others [4h] and Ludlam and Henderson.[5] (*e*) Faber, H. K., and Clark, E. B.: Prevention and Treatment of Thrush (Oidial Stomatitis), Am. J. Dis. Child. **34**:408-417 (Sept.) 1927. (*f*) Plass, E. D.; Hesseltine, H. C., and Borts, I. H.: Monilia Vulvovaginitis, Am. J. Obst. & Gynec. **21**:320-334 (March) 1931. (*g*) Hesseltine, H. C.; Borts, I. C., and Plass, E. D.: Pathogenicity of Monilia (Castellani) Vaginitis and Oral Thrush, ibid. **27**:112-116 (Jan.) 1934. (*h*) Bland, P. B.; Rakoff, A. E., and Pincus, I. J.: Experimental Vaginal and Cutaneous Moniliasis: Clinical and Laboratory Study of Certain Monilias Associated with Vaginal, Oral and Cutaneous Thrush, Arch. Dermat. & Syph. **36**:760-780 (Oct.) 1937. (*i*) Woodruff, P. W., and Hesseltine, H. C.: Relationship of Oral Thrush to Vaginal Mycosis and Incidence of Each, Am. J. Obst. & Gynec. **36**:467-471 (Sept.) 1938.

5. Ludlam, G. B., and Henderson, J. L.: Neonatal Thrush in a Maternity Hospital, Lancet **1**:64-70 (Jan. 17) 1942.

6. Hesseltine, H. C.: Vulval and Vaginal Mycosis and Trichomoniasis, Am. J. Obst. & Gynec. **40**:641-646 (Oct.) 1940.

a study conducted in retrospect from available hospital records, the reliability of which is often open to question.

Ludlam and Henderson [5] observed moniliasis in 18.3 per cent of the infants they studied, and Haler,[7] in 20 per cent. These rates are comparable to the incidence of 18.7 per cent in the present series. It seems that when the mouths of newborn infants are carefully and repeatedly inspected, the incidence of moniliasis is higher than that which is reported from nurseries in general.

It is significant that in each instance in which M. albicans was isolated from the mouth of a newborn infant oral thrush developed. This work confirms the report of Ludlam and Henderson.[5] It became evident that oral thrush could be anticipated on the basis of a mycologic report of the presence of M. albicans. Six infants were therefore isolated as soon as M. albicans was identified. In each instance clinical disease developed within two to three days. It would seem advisable to isolate infants by such a schedule if it were practical to make mycologic studies routinely.

M. albicans is not part of the normal cutaneous flora. Benham and Hopkins [8] stated the belief that it is saprophytic in the intestinal tract and expressed the opinion that this may be a source of infection to predisposed areas of skin, resulting in definite cutaneous monilial lesions. Ludlam and Henderson [5] observed M. albicans in the stools of infants with oral moniliasis. These aspects of monilial infection have not been investigated in the present study.

SUMMARY AND CONCLUSIONS

In this series of infants oral thrush developed in each instance in which Monilia (Candida) albicans was found in the mouth of a newborn infant but in no instance when only other forms of yeast were present. Furthermore, M. albicans was isolated, without exception, from the mouth of each infant who had oral thrush. After an infant had had clinical thrush, M. albicans was harbored in the mouth for a variable period, even after all clinical evidence of the disease had disappeared.

Oral thrush appeared earlier and more frequently in infants whose mothers had vaginal moniliasis. The possibility is suggested that the infection might occur by contacts other than directly from the vagina, since the period after birth before the oral lesions were manifest was longer than the known incubation period for monilial infection. Intimate postpartum contact, as at nursing time, may be significant for the introduction of M. albicans into the mouth of the infant from the mother, whose skin, clothing and bed linen may be contaminated. It has been suggested that the disease may be prevented by prohibiting any contact of an infant with an infected mother during the immediate postpartum period.

Of twenty-four cultures of material from the mouths of newborn infants which contained yeast, twenty yielded M. albicans. Thus, for practical purposes, it would appear justified to consider a direct smear containing yeast as positive evidence of the presence of M. albicans if the material was taken from a mouth which appeared clinically to have early thrush and, on the basis of such evidence, to institute treatment immediately.

On the basis of this investigation it is recommended that all infants born of mothers with vaginitis due to M. albicans and all infants from whom oral cultures show M. albicans, even in the absence of clinical evidence of thrush of the mouth, be isolated as a prophylactic measure against the spread of the infection in the nursery for newborn infants. It would also seem advisable to institute treatment immediately for infants in these two categories, even in the absence of clinical signs of thrush, in order to prevent its development. Prophylactically it is important in antepartum care to determine the presence of M. albicans in the vagina of a pregnant woman as early as possible and to institute appropriate treatment during the pregnancy in order to reduce the possibility of the transfer of the infection to the newborn infant.

7. Haler, D. H.: Bronchomoniliasis, Brit. M. J. **1**:1052-1053 (June 4) 1932.

8. Benham, R. W., and Hopkins, A. M.: Yeastlike Fungi Found on Skin and in Intestines of Normal Subjects: Survey of One Hundred Persons, Arch. Dermat. & Syph. **28**:532-543 (Oct.) 1933.

The members of the Department of Obstetrics obtained the vaginal specimens from the mothers before the delivery of the infants included in this study.

Mrs. Grace F. Howell gave technical assistance in the study.

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ATELECTASIS COMPLICATING ACUTE POLIOMYELITIS WITH INVOLVEMENT OF RESPIRATORY MUSCLES

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Several years after the introduction of the mechanical respirator Smith [1] called attention to the fact that one third of the patients who had been in respirators and were discharged to various orthopedic hospitals and convalescent homes died with infections of the respiratory tract, reported in the hospital records as bronchopneumonia. A review of the records of 2 such patients and postmortem studies on a third led him to believe, however, that the pulmonary infections develop secondarily to atelectasis produced by obstruction of the bronchi by unexpelled exudate. Coryllos and Birnbaum [2] had previously emphasized the importance of the role of atelectasis in the development of pneumonia, and there has since developed a considerable interest with regard to the mechanical effects of obstructing bronchial exudate in infections of the respiratory tract in general.

In paralysis of the respiratory muscles due to poliomyelitis a number of factors predispose to the development of atelectasis. Foremost among them is the reduction of vital capacity which occurs in this condition. Normally, vital capacity is controlled not only by the tonus of the muscles of respiration but by the tonus of the skeletal muscles of the body as a whole. Decreased general muscular tonus is, for example, an important factor in the development of atelectasis following anesthesia and surgical procedures, a fact originally brought out by Henderson [3] and more recently reemphasized by Molony [4] in a review of the causative factors in the production of postoperative collapse in children. Brennemann [5] expressed the belief that any clinical condition associated with generalized weakness may, in fact, constitute a potential cause for massive pulmonary collapse and cited as observed examples such conditions as postdiphtheritic paralysis, pseudohypertrophic muscular dystrophy, poliomyelitis and acrodynia. In poliomyelitis the reduction of vital capacity is thus not merely the result of direct involvement of the muscles of respiration; it must be influenced by a general loss of muscle tonus consequent on the extensive involvement of muscles that invariably coexists.

Another important factor in the production of atelectasis in poliomyelitis is related to the integrity of the cough mechanism. The ability to cough in these patients is impaired in proportion to the extent of the pathologic process. Failure to rid the bronchial airways of exudate leads to bronchial occlusion and atelectasis. Should the obstructing material contain infective agents, as it invariably does, the situation is then fertile for the development of secondary pneumonia. Besides actual paralysis of the muscles concerned with the act of coughing, there is poor bronchial drainage from the hypoventilated pulmonary tissue present in such conditions. Actual reduction in the size and motility of the bronchi occurs in hypoventilated lungs, and this reduction, together with a decrease in the amount of available air that can be expelled by coughing reduces the effectiveness of expectoration.[6] Coughing is impossible when the controlling reflex arc is broken by destruction of the cells of the anterior horn, and death results from suffocation from gradually accumulating mucus.[1]

It is thus apparent that in poliomyelitis with paralysis of the respiratory muscles there exists a precarious condition which constitutes a constant threat of the development of grave pul-

From the Northern Michigan Children's Clinic.

1. Smith, E.: Respiratory Failure and the Drinker Respirator in Poliomyelitis, J. A. M. A. **100**:1666 (May 27) 1933.

2. Coryllos, P. N., and Birnbaum, G. L.: Lobar Pneumonia Considered as Pneumococcic Lobar Atelectasis of the Lung: Bronchoscopic Investigation, Arch. Surg. **18**:190 (Jan.) 1929.

3. Henderson, Y.: (*a*) Reasons for the Use of Carbon Dioxide with Oxygen in the Treatment of Pneumonia, New England J. Med. **206**:151 (Jan. 28) 1931; (*b*) Wesley M. Carpenter Lecture: Atelectasis, Massive Collapse and Related Post-Operative Conditions, Bull. New York Acad. Med. **11**:639 (Nov.) 1935.

4. Molony, C. J.: Postoperative Pulmonary Collapse in Childhood, Am. J. Dis. Child. **66**:280 (Sept.) 1943.

5. Brennemann, J.: Bronchiectasis as a Pediatrician Sees It, Dis. of Chest **9**:39 (Jan.-Feb.) 1943.

6. Haight, C., and Ransom, H. K.: Observations on Prevention and Treatment of Postoperative Atelectasis and Bronchopneumonia, Ann. Surg. **114**:243 (Aug.) 1941.

monary complications. For a patient already encumbered with serious liabilities, the advent of such complications may well spell disaster. It is therefore of interest to record 4 instances in 3 of which unexpected recovery took place. At the same time, it is of further interest both to trace the development of the pulmonary complications and to appraise the relative importance of the factors involved in their outcome.

REPORT OF CASES

CASE 1.—V. C., a boy 5 years of age, was admitted to the hospital on Oct. 3, 1940. He had been ill two days. On admission, he had a temperature of 101.4 F. He was drowsy and had difficulty in swallowing. Respiration was shallow and chiefly abdominal. The child had loss of function of both the upper and the lower extremities. His condition seemed precarious. Although he had bulbar symptoms as well as evidence of peripheral respiratory failure, it was thought advisable to give him a trial in a mechanical respirator. Gradual improvement followed during the next few days. By the seventh day he was able to talk and to swallow fluids and by the tenth day he could eat soft foods. By the third week he improved to the extent that he could be permitted out of the respirator for forty-five minutes a day, and after six days the time was increased to seventy-five minutes. On December 18 an infection developed in the upper respiratory tract. He was given 3 Gm. of sulfathiazole daily for two days and showed improvement. A roentgenogram of the chest taken at this time (fig. 1 *A*) showed paralysis of the right side of the diaphragm, as indicated by its distinct elevation. Evident also was considerable reduction in the volume of the right lung. The mediastinal structures, however, were in their normal position, and there was no evidence of atelectasis.

On Jan. 7, 1941, three months after admission to the hospital, the patient suddenly began to have difficulty in breathing. He had difficulty in coughing and was unable to get rid of mucus in his throat. On the second day his temperature rose to 101.2 F. and his pulse became rapid. On the third day considerable mucus accumulated in his throat; he made poor attempts to cough, and the attempts were frequently accompanied by vomiting. By the fourth day his condition had grown worse. Three grams of sulfathiazole daily were prescribed at this time. The patient's temperature rose to 102.2 F., and cyanosis and increased dyspnea developed. The boy appeared listless. A roentgenogram of the chest (fig. 1 *B*) showed complete atelectasis of the right lung, with shifting of the mediastinal structures into the right side of the thorax. The patient's condition grew progressively worse, and he died the following day (January 11).

CASE 2.—D. C., a boy 8 years of age, was admitted to the hospital on Aug. 28, 1940, with evidence of peripheral respiratory failure. He had urinary retention and distinct loss of function of both upper and lower extremities. He was put into a mechanical respirator, which brought immediate relief. Six days after admission he was allowed out of the respirator for forty-five minutes, and by the tenth day the time was increased to two hours. On the patient's seventeenth day in the hospital the use of the respirator was discontinued. Four days later (Sept. 19, 1940), three weeks after the patient was admitted to the hospital, dyspnea, cyanosis, a rapid pulse rate and an elevated temperature (101.8 F.) developed. The patient was unable to cough. Sulfathiazole, 3 Gm. daily, was prescribed, and the child was kept continuously in the respirator. The following day a roentgenogram of the chest (fig. 2 *A*) disclosed a homogeneous area of increased density involving the entire right lung, with shifting of the mediastinal structures into the right side of the thorax, indicative of complete collapse of the right lung.

Steady improvement took place during the ensuing week. A roentgenogram of the chest, taken five days after the onset of pulmonary complications (fig. 2 *B*), showed that the mediastinal structures had returned to the midline position. There was a homogeneous shadow in the lower lobe of the right lung, probably representing a resolving pneumonic process. By the eleventh day, a roentgenogram of the chest (fig. 2 *C*) appeared normal. The administration of sulfathiazole was maintained for a period of two weeks. The time spent in

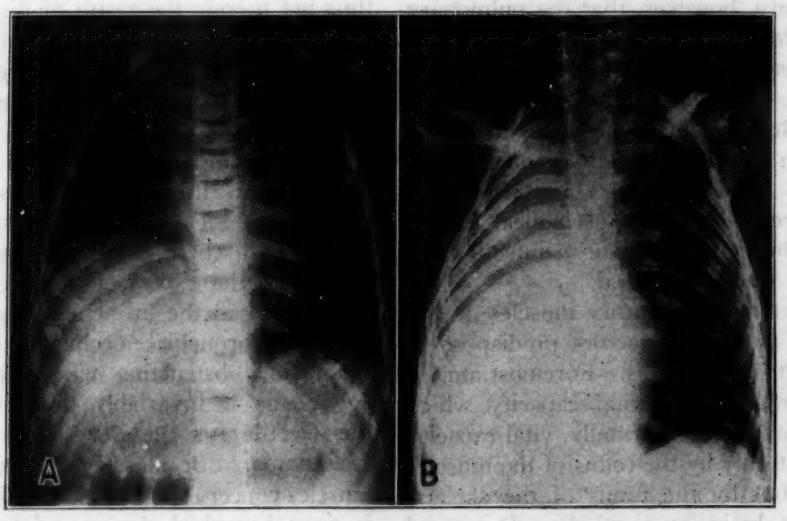

Fig. 1 (case 1).—Roentgenograms of V. C., a boy 5 years of age; *A*, eleven weeks after onset of poliomyelitis, showing paralysis of the right dome of the diaphragm, and *B*, the day before the patient died, three months after onset of poliomyelitis, showing complete atelectasis of the right lung.

the respirator was gradually reduced, and the use of the respirator was again discontinued five weeks after the onset of pulmonary complications.

CASE 3.—F. P., a boy 4 years of age, was admitted to the hospital on July 30, 1940 with evidence of peripheral respiratory failure. He exhibited loss of function of all the extremities, with greater involvement of the upper extremities. He was immediately put into a mechanical respirator. On September 11, six weeks after the patient was admitted to the hospital, an infection developed in the upper respiratory tract. At this time, the patient was still kept continuously in the respirator. Two days later his temperature rose to 102.8 F. Sulfathiazole, 2 Gm. daily, was prescribed. The next day dyspnea, cyanosis and a rapid pulse rate developed. Mucus accumulated in the patient's throat, and he was unable to cough. Physical examination revealed flattening of the upper part of the left side of the chest anteriorly. The apex beat was felt at the anterior axillary region in the fifth left intercostal space. There was suppression of respiratory sounds over practically the entire left side of the chest; no rales were present. A diagnosis of atelectasis of the left lung was confirmed by a roentgenogram of the chest (fig. 3*A*). The administration of sulfathiazole was maintained for two weeks. Improvement in the patient's condition was gradual. By October 4, three weeks after the onset of pulmonary complications, a roentgenogram of the chest (fig. 3*B*) showed obvious improvement. The left lung appeared clear. The mediastinal structures were almost back to the normal position. On October 7 the patient was allowed out of the respirator for thirty minutes, and this period was gradually increased, so that by October 19, six weeks

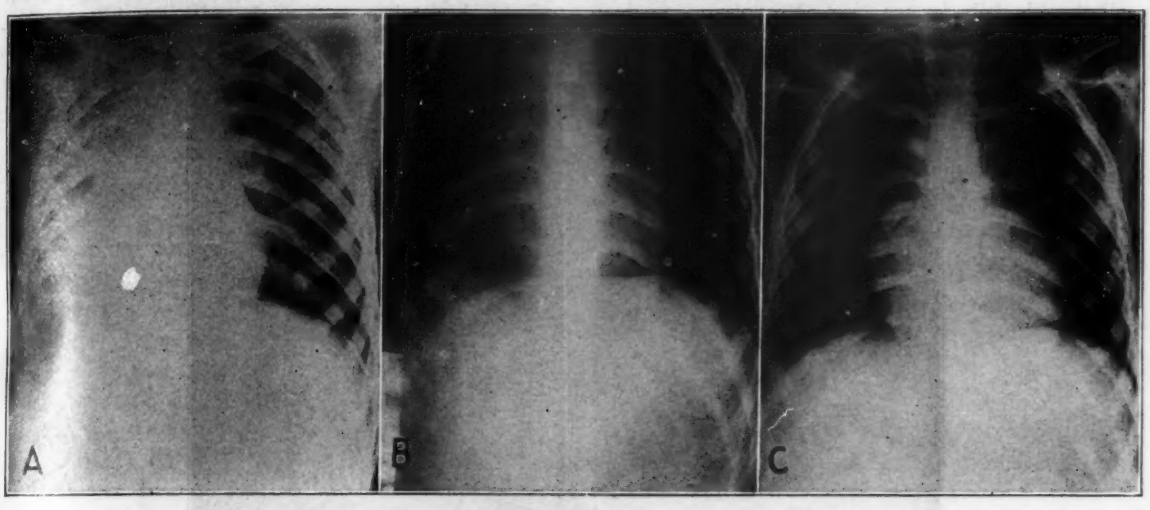

Fig. 2 (case 2).—Roentgenograms of D. C., a boy 8 years of age; *A*, three weeks after onset of poliomyelitis, showing atelectasis of the right lung, *B*, five days later, showing clearing of the atelectasis with complete return of the mediastinal structures to their midline position (the homogeneous shadow in the lower part of the right lung probably representing a resolving pneumonic process) and *C*, sixteen days after onset of pulmonary complications, showing normal appearance of the lungs.

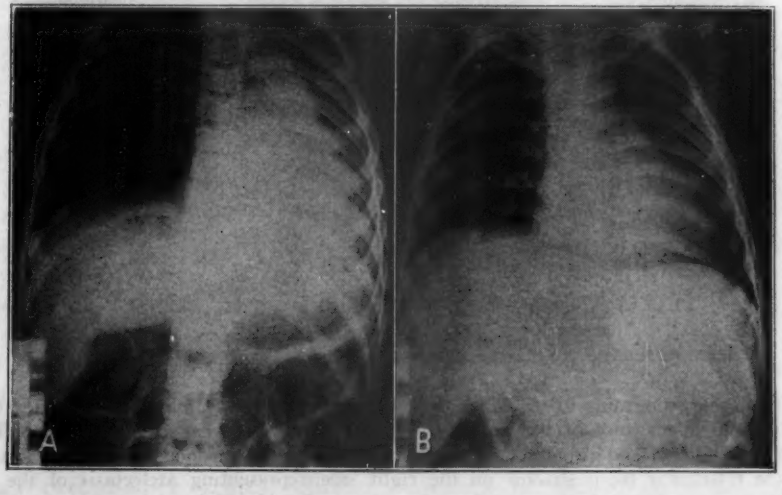

Fig. 3 (case 3).—Roentgenograms of F. P., a boy 4 years of age; *A*, six weeks after onset of poliomyelitis, showing atelectasis of the left lung following the occurrence of an infection of the upper respiratory tract, and *B*, three weeks later, showing clearing of the atelectasis.

after the onset of pulmonary complications, the use of the respirator was discontinued.

CASE 4.—A. M., a boy 12 years of age, was admitted to the hospital on Oct. 14, 1940 with loss of function of both arms and both legs. He had evidence of serious paralysis of the respiratory muscles. Great relief was obtained immediately by the use of the respirator. On Jan. 27, 1941, an infection developed in the upper respiratory tract, and the patient was given 3 Gm. of sulfathiazole daily for ten days. No pulmonary complications developed. During that time the patient was in the respirator continuously, except for short periods, up to thirty minutes daily. A roentgenogram of the chest taken April 17, 1941 (fig. 4 *A*) showed that the lungs were well aerated and the mediastinal structures in the normal position. On Oct. 31, 1941, approximately one year after admission, at which time he was still kept practically continuously in the respirator, the patient experienced some difficulty in coughing up mucus from his throat. He had no apparent evidence of infection of the respiratory tract at this time. The next day his temperature rose slightly, and by November 2 it had reached 102.4 F. and his pulse rate had increased to 140 per minute. Sulfathiazole was administered, starting with 1 Gm., followed by 0.5 Gm. every four hours. The boy had increasing cyanosis and dyspnea, which became severe by November 5. Considerable mucus accumulated in his throat, and he exhibited great difficulty in coughing. A roentgenogram of the chest taken on Nov. 7, 1941 (fig. 4 *B*), showed diffuse increased density of the right lung, with shifting of the mediastinal structures toward the right side, indicative of atelectasis.

The patient's condition improved gradually. He was given sulfathiazole until November 18, at which time gross hematuria developed. Sulfadiazine was then substituted in equivalent dosage, and the hematuria disappeared. By November 27, one month after the onset of pulmonary complications, the patient's condition was sufficiently improved to permit his being out of the

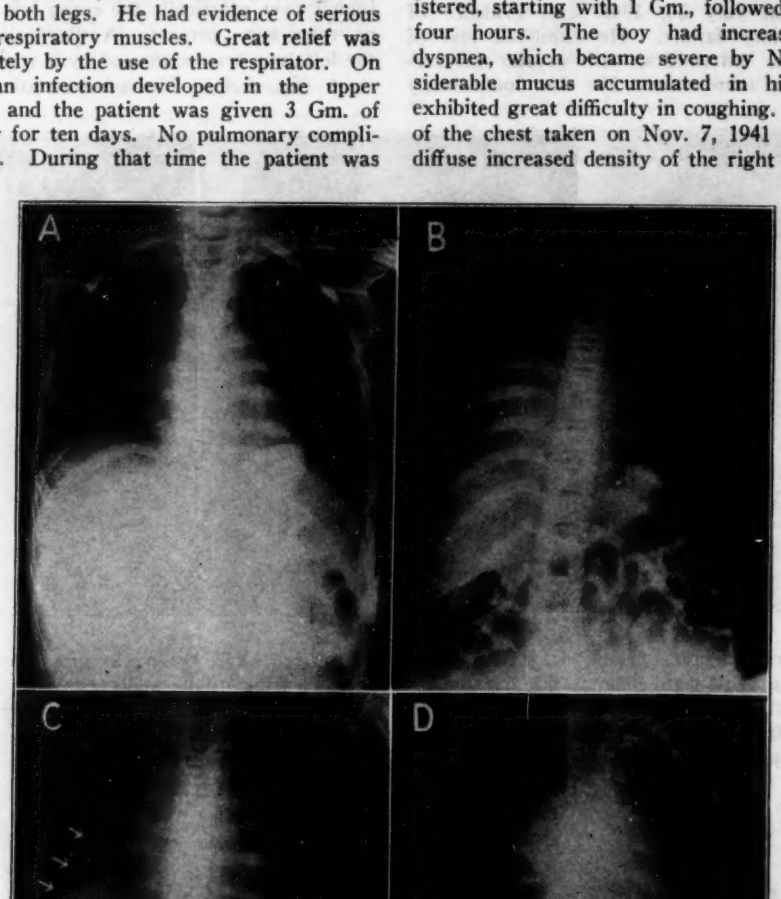

Fig. 4 (case 4).—Roentgenograms of A. M., a boy 12 years of age; *A*, nine months after the onset of poliomyelitis, showing normal appearance of the lungs, *B*, approximately one year after onset of poliomyelitis, showing atelectasis of the right lung; *C*, one month later, showing shift of the mediastinal structures toward the normal midline position (the triangular basal shadow on the right side representing atelectasis of the lower lobe which gradually cleared spontaneously) and *D*, approximately six months later, showing reaeration of the lung. (The apparent widening of the mediastinum in *C* and *D* is due to distortion, as a result of obtaining the films with a portable x-ray machine.)

respirator with comfort for short periods. A roentgenogram of the chest taken at this time revealed the presence of atelectasis in the region of the base of the right lung. The administration of sulfadiazine was discontinued on November 29. The patient continued to progress favorably. Another roentgenogram of the chest taken on Dec. 8, 1941 (fig. 4*C*), showed the triangular shadow characteristic of basal atelectasis of the right lung, although the mediastinal structures had moved toward their normal positions. Gradual reaeration of the atelectatic lobe followed. A roentgenogram taken nearly seven and a half months after the onset of pulmonary complications (fig. 4*D*) showed the lungs to be practically clear.

COMMENT

It is interesting to note that in all of the patients atelectasis developed after the acute phase of the disease had passed, the pulmonary complications occurring from three weeks to one year after the admission of the patient to the hospital. Three of the patients were still in the respirator, and for the fourth patient the use of the respirator had been discontinued only four days prior to the occurrence of atelectasis. All the patients had extensive paralysis of all the extremities in addition to involvement of the muscles of respiration, the resulting general weakness constituting, in itself, a predisposition to the development of atelectasis.

The relation of preceding infection of the respiratory tract to the occurrence of atelectasis seemed clearcut in only 1 of the patients (F. P., case 3), the onset of the infection of the upper respiratory tract occurring two days prior to atelectasis. In 2 of the patients (V. C., case 1, and A. M., case 4), the development of pulmonary complications was preceded, several days earlier, by difficulty in clearing the throat of mucus, without, however, any appreciable evidence of infection of the upper respiratory tract. In the fourth patient (D. C., case 2) atelectasis occurred rapidly and without warning. In all 4 patients serious impairment of the cough mechanism was apparent, and it seems more than likely that bronchostenosis, atelectasis and secondary pneumonia were in a great measure direct consequences of the loss of this function.

The fully developed pulmonary complication in these patients presented a critical clinical picture characterized by fever, dyspnea, cyanosis, rapid pulse, serious impairment of the cough mechanism and prostration. These alarming signs undoubtedly represent the development of pneumonia superimposed on antecedent atelectasis. In 3 of the patients (V. C., F. P. and A. M., cases 1, 3 and 4) this critical picture developed relatively gradually; in the remaining patient (D. C., case 2), it appeared within a short time.

The recovery of 3 of the 4 patients from a condition which appeared overwhelmingly against the chance of survival is of special interest. As an indication of their incapacitation, it should be emphasized that these 3 patients were still being kept practically continuously in the respirator at the time of the occurrence of the pulmonary complications.

It did not appear likely that the continued use of the mechanical respirator, together with any natural factors aiding recovery, could have sufficed to produce the favorable outcome in the 3 patients. Since the clinical course strongly indicated that pneumonia following atelectasis was chiefly responsible for the imminently dangerous aspects of the pulmonary complications, it seems reasonable to believe that recovery, with spontaneous clearing of the atelectasis, was primarily dependent on the early favorable response of the patients to treatment with sulfonamide compounds.

The liability to grave pulmonary complications being so great in patients with poliomyelitis with impaired function of the respiratory muscles, it is imperative to guard these patients against all possible hazards. It is clear that foremost among the hazards are infections of the respiratory tract, even of the mildest sort, and avoidance of exposure to them is obviously a vital precaution. The administration of sulfonamide drugs at the earliest signs of infection of the respiratory tract in these patients appears to offer an important prophylactic measure against more serious developments. For 2 of the patients (V. C. and A. M., cases 1 and 4), for example, chemotherapy was thus employed early in the course of infections of the upper respiratory tract, and no pulmonary complications resulted.

Another important preventive measure is the careful gaging of the indications for removal of the patient from the respirator. Smith [1] emphasized that the ability to breathe freely and without effort is in itself not an indication. The ability to cough is the prime indication. Patients removed from the respirator in the absence of ability to cough may later have atelectasis. In severe poliomyelitis this may mean the use of the respirator for many months or even permanently. Wilson [7] advocates the intermittent use of the respirator, over periods of months, for purposes of graduated rest and recommends increasing the time spent in the respirator by patients with limited vital capacity

7. Wilson, J. L.: The Use of the Respirator in Poliomyelitis, New York, National Foundation for Infantile Paralysis, Inc., 1942.

in whom infections of the respiratory tract develop.

The early use of bronchoscopy for the relief of bronchostenosis can, in the hands of a practiced operator, no doubt, minimize pulmonary complications in many such instances and, in retrospect, might have been tried with advantage for the patients reported here. That atelectasis could have cleared spontaneously in patients already so seriously handicapped is surprising, even with the early control of the pneumonic process by the use of sulfonamide compounds.

In the light of the foregoing discussion, two items are noteworthy with regard to the child who died. In the first place, administration of sulfathiazole was instituted relatively late in the course of the pulmonary complications. Secondly, the use of the respirator had been recently, although gradually, discontinued. Since impaired ability to cough became prominent during the pulmonary complications, it can be assumed that removal of the patient from the respirator may have been premature and may have thereby contributed to the development of atelectasis.

SUMMARY

There exists in poliomyelitis with involvement of the respiratory muscles a constant threat of the sequential development of bronchostenosis, atelectasis and secondary pneumonia, primarily due to the presence of the predisposing factors of diminished vital capacity of the lungs and impaired efficiency of the cough mechanism. This threat of serious pulmonary complications becomes imminent with the occurrence of infection of the respiratory tract.

Of 4 patients with atelectasis complicating poliomyelitis with paralysis of the muscles of respiration 3 recovered. The favorable outcome in these patients followed the occurrence of a critical clinical picture, undoubtedly due to the development of secondary pneumonia. Recovery appeared to depend on the favorable effect of treatment with sulfonamide compounds on the pneumonic process, permitting ultimate spontaneous clearing of the atelectasis.

In considering prophylaxis against pulmonary complications, avoidance of exposure to infections of the respiratory tract is of utmost importance. With the occurrence of such infections, the early institution of chemotherapy may be effective in preventing the development of more serious complications. The continued use of the mechanical respirator under such circumstances is essential. Although not employed for the patients reported here, the early use of bronchoscopy for the relief of bronchial occlusion may minimize pulmonary complications under such circumstances. It is of unusual interest that in patients already so seriously handicapped by poliomyelitis spontaneous clearing of atelectasis is possible.

Northern Michigan Children's Clinic.

ROENTGENOGRAMS OF THE CHEST TAKEN DURING PERTUSSIS

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Roentgenograms of the chest taken during the course of pertussis were first described by Gottlieb and Möller,[1] more than twenty years ago. The subject has recently been excellently reviewed by Lapin [2] and Maggi.[3] Often they found no clinical evidence or physical sign corresponding to the changes noted in roentgenograms of the lungs. Careful pathologic studies of lungs of children who died of pertussis were made by Feyrter,[4] Hayakawa [5] and others. These lungs on gross examination showed scattered areas of consolidation and atelectasis. Some authors emphasized enlargement of the lymph nodes in the hilar region as a contributing cause of symptoms. Histologic examination showed mainly peribronchial infiltration, with infiltration of the adjacent alveoli and interstitial thickening of the alveolar walls. Areas of atelectasis and emphysema were also seen frequently. The changes seen in roentgenograms were therefore thought to be caused by the pulmonary conditions previously described plus mediastinal lymphadenitis (Smith [6]).

At the Willard Parker Hospital our necropsy observations for children who died while they had pertussis were similar to those already described. Enlargement of the tracheobronchial lymph nodes, however, was observed infrequently (Dolgopol [7]). The absence of lymphadenopathy was noted both in children who had severe pulmonary symptoms and in children in whom pulmonary symptoms were not predominant. The latter group included children who died during a convulsive seizure.

Some years ago Kohn and Koiransky [8] reported that a roentgen study showed that the tracheobronchial lymph nodes were usually enlarged in measles. This enlargement was demonstrated by taking roentgenograms not only in the usual position but in the lateral position. It was decided to repeat this procedure for patients with pertussis.

PROCEDURE

Whenever possible, roentgenograms were taken every few days while the patient stayed in the hospital. A physical examination was made at the time that each roentgenogram was taken. The exposures were made at a distance of 52 inches (132 cm.) with a 60 kilowatt, 250 milliampere current. The time of exposure was one fortieth of a second. The roentgenograms were taken in the posteroanterior position and, whenever possible, in the direct right lateral position also. By utilizing the lateral position a clearer visualization of the lymph nodes of the posterior mediastinum and of those located in the hilar region, at the bifurcation of the trachea, was gained. Lateral exposures also brought out more clearly involvement of the lung in the region of the interlobar fissure. Nearly all roentgenograms were taken with the subject in the sitting position. We feel reasonably certain that none of the children here reported on had been infected with tuberculosis.

The majority of the children were admitted to the hospital ten to twenty-one days after the onset of symptoms. Pertussis is not usually suspected until a child has been coughing for about two weeks.

OBSERVATIONS

We divided the patients into three groups: first, those who had no fever before or during

From the Willard Parker Hospital for Contagious Diseases.

1. Gottlieb, K., and Möller, B.: Ueber Saüglings-Pertussis, Jahrb. f. Kinderh. **100**:222 (Dec.) 1922.

2. Lapin, J. H.: Whooping Cough, Springfield, Ill., Charles C Thomas, Publisher, 1943.

3. Maggi, R.: El "pulmón coqueluchoso:" Su imagen radiológica, Rev. Asoc. méd. argent. **55**:427 (June 15-30) 1941.

4. Feyrter, F.: Ueber die pathologische Anatomie der Lungenveränderungen beim Keuchhusten, Frankfurt. Ztschr. f. Path. **35**:213, 1927.

5. Hayakawa, T.: Studien über Keuchhustenpneumonie: I. Pathologische Anatomie der Keuchhustenlunge nebst einer experimentellen Studie über das Röntgenbild der Keuchhustenlunge beim Menschen, Ztschr. f. Kinderh. **47**:532, 1929.

6. Smith, L. W.: The Pathological Anatomy of Pertussis with Special Reference to Pneumonia Caused by Pertussis Bacillus, Arch. Path. **4**:731 (Nov.) 1927.

7. Dolgopol, V.: Personal communication to the authors.

8. Kohn, J. L., and Koiransky, H.: Further Roentgenographic Studies of the Chests of Children During Measles, Am. J. Dis. Child. **46**:40 (July) 1933.

the time they were in the hospital; second, those who during the course of the attack had a low grade fever for one to three days, and, third, those who during the course of the attack had a temperature of over 101 F. for two days or longer.

TABLE 1.—*Severity of Pertussis in Relation to the Degree of Fever*

Degree of Fever	Number of Children	Severity of Attack		
		Mild	Moderate	Severe
None	154	46	83	25
Low	15	6	5	4
High	53	1	15	37

The first group of patients, those who had no fever, consisted of 154 children. Clinically, the pertussis was considered mild in 46 children (29.8 per cent), moderately severe in 83 children (53.8 per cent) and severe in 25 children (16.2 per cent) (table 1).

Roentgenograms taken in the posteroanterior position were considered normal in 68 children (44.16 per cent). In 48 children (31.6 per cent) the roentgenograms showed increased pulmonary markings without areas of pulmonary consolidation; there were coarse linear markings extending from the hilar region toward the diaphragm or extending outward toward the periphery. The roentgenograms showed the presence of pulmonary consolidation in 38 children (24 per cent) (table 2). The frequency of the occurrence of

TABLE 2.—*Roentgenologic Changes in the Lungs of Children Who Had No Fever During Pertussis in Relation to Age*

Age, Yr.	Number of Children	Roentgenograms		
		Normal	Increased Pulmonary or Hilar Markings	Pneumonic Infiltration
Under 1	27	19	5	3
1 to 2	31	12	10	9
2 to 3	23	8	8	7
3 to 4	23	9	12	2
4 to 5	15	4	6	5
5 to 6	10	4	1	5
6 to 7	16	8	5	3
7 to 9	9	4	1	4
Total	154	68	48	38

pulmonary consolidation in this group was approximately the same as reported by other observers (Hünermann [9] and Wildtgrube [10]).

9. Hünermann, C.: Die Röntgenologie der Keuchhustenlunge und ihre Bedeutung für die Klinik. Monatschr. f. Kinderh. **57**:36 (Feb. 16) 1933.

10. Wildtgrube, F.: Einige Fragen aus der Keuchhusten pathologie, Ztschr. f. Kinderh. **50**:152, 1930.

Of the 38 children of the first group who showed pulmonary consolidation, 10 were considered mildly ill, 21 moderately ill and 7 severely ill (table 3). There was infiltration of the upper lobe in only 3 patients. The consolidation was located in the hilar region 14 times and was present at the base of the lung 30 times. In several children both regions, hilar and basal, were involved.

The cardiophrenic angles were the common sites of pulmonary opacity. The roentgenographic appearance can be described as follows: There was a diffuse, irregularly shaped opacity

TABLE 3.—*Severity of Pertussis in Relation to the Degree of Fever in Children with Pneumonic Consolidation*

Degree of Fever	Number of Children	Severity of Attack		
		Mild	Moderate	Severe
None	38	10	21	7
Low	11	3	4	4
High	43	0	11	32

over the base of the pulmonary field, partly obscuring the diaphragmatic shadow and often concealing the lower portion of the cardiac border. This border frequently appeared as an irregular fluffy line. The shape of the opacity was often triangular, the base of the triangle being on the plane of the diaphragm (fig. 1 *A*). This triangular shadow has been emphasized by Debré [11] and others. The significance of the shadow will be discussed later.

Roentgenograms in the direct lateral position were made for 35 children, 21 of whom were under 5 years of age. In this group 15 patients were considered mildly ill, 13 moderately ill and

TABLE 4.—*Incidence of Opacities in Hilar Region and Middle Lobe Area, as Shown By Direct Lateral Exposures in Relation to Degree of Fever*

Degree of Fever	Number of Lateral Roentgenograms	Dense Opacities in Hilar Region	Triangular Opacity
None	35	7	3
Low	6	1	3
High	20	1	7

7 severely ill. In 23 there was no evidence of pneumonic infiltration. Of the patients for whom the roentgenograms showed consolidation, the illness was considered mild in 5, moderate in 3 and severe in 5.

11. Debré, R.; Lamy, M.; Mignon, M., and Welti, J. J.: Le "poumon coquelucheux" et son image radiologique, Presse méd. **46**:1011 (June 25) 1938.

Enlarged, dense, irregular opacities in the hilar region were seen in only 7 of the children in the first group (table 4); in the others only small, indefinite opacities were seen in this area. An area of increased opacity was seen in the roentgenograms of 5 children who showed no clinical evidence of pulmonary infiltration. The infrequent occurrence of enlarged lymph nodes was in contrast with the condition found in measles.

In 3 children roentgenograms taken in the lateral position showed a large homogeneous triangular opacity between the major and minor fissures of the right lung, which enclose the middle lobe (table 4). The apex of the triangle pointed posteriorly. The fissure between the upper and middle lobes of the right lung was often depressed, and the heart was drawn to the right side. This condition was interpreted as being due to atelectasis plus pneumonic infiltration of the middle lobe of the right lung (fig. 1 *B*). This shadow was present only in children who in the posteroanterior view showed evidence of pulmonic consolidation in the region of the cardiophrenic angle. Subsequently, roentgenograms showed mottling in the triangular shadow, and the middle lobe assumed its usual position within about fourteen days and there were no resultant abnormalities (fig. 3). We hope to present a more detailed study of the resolution of the atelectasis and pneumonic infiltration of the middle lobe in a later publication.

The triangular shadow is due to involvement of the middle lobe of the right lung by pneumonia, atelectasis or both. Sounds indicating involvement of the middle lobe of the right lung are best heard low in the right axilla between the posterior and the anterior axillary line. Although there was roentgen evidence of involvement of the right middle lobe, often no physical signs were elicited; at other times there were dulness and diminished breathing. We heard no bronchial breathing.

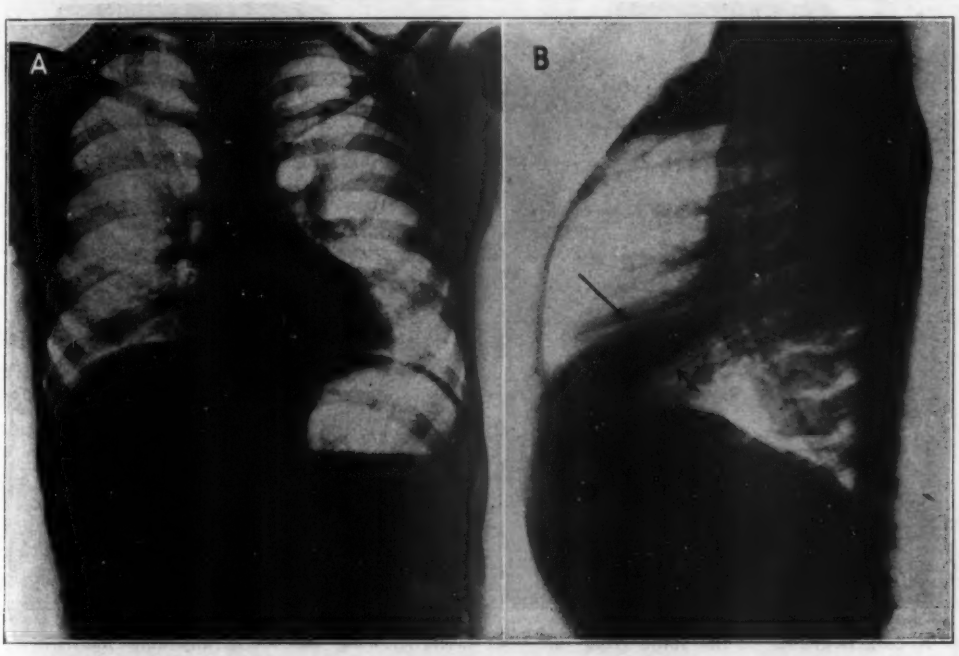

Fig. 1.—*A*, posteroanterior roentgenogram of a 7 year old girl taken three weeks after onset of cough (two days of fever before admission), showing a nonhomogeneous shadow, roughly triangular, in the medial portion of the lower pulmonary field, extending outward at the base to within 1 inch (2.5 cm.) of the axillary border. There are also some infiltrations in the lower lobe of the left lung, particularly behind the heart.

B, direct right lateral roentgenogram of the same child, showing a dense homogeneous triangular shadow in the area corresponding to the middle lobe of the right lung. The short fissure is depressed, suggesting atelectasis. There are nonhomogeneous shadows above and below the triangular shadow, which probably represent infiltrations of the lower lobe and upper lobe of the same lung.

The second group, patients with low grade fever, consisted of 15 children. The illness was considered mild in 6 of these children, moderately severe in 5 and severe in 4 (table 1). We found increased pulmonary markings in the roentgenograms of 2 children and evidence of pneumonic infiltration in those of 11 (table 5). Of these 11 children, 3 were mildly, 4 were moderately and 4 were severely ill (table 3).

Roentgenograms in the lateral position were taken for 6 patients in this group. Increased opacities in the region of the hilar lymph nodes were noted in 1 patient. A homogeneous triangular shadow in the region of the middle lobe of the right lung was noted in 3 children (table 4).

The third group consisted of 53 children who during the course of their pertussis had a temperature of 101 F. or over. Successive roentgenograms were taken twice for 12 children and 3 or more times for 25 children. In this group 29 children were 2 years of age and under, 12 were between 3 and 4 years and 12 were over 4 years. Clinically, only 1 child was considered to have mild pertussis. Fifteen children had pertussis of moderate severity, and 37 were classified as severely ill (table 1).

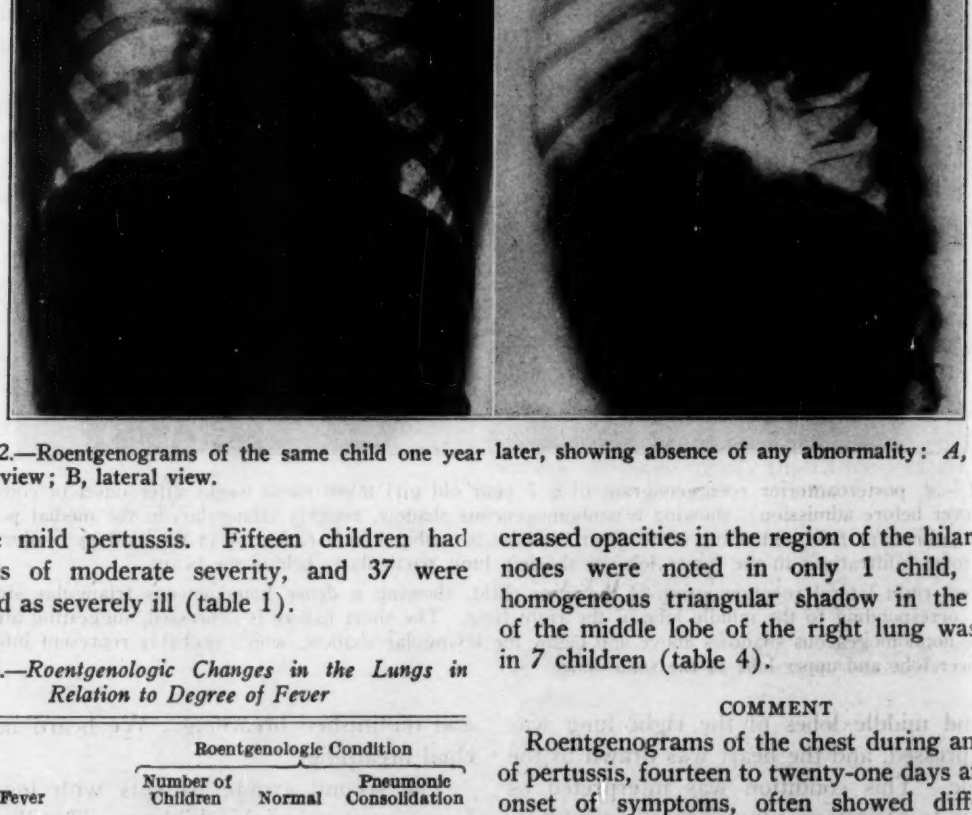

Fig. 2.—Roentgenograms of the same child one year later, showing absence of any abnormality: *A*, postero-anterior view; B, lateral view.

TABLE 5.—*Roentgenologic Changes in the Lungs in Relation to Degree of Fever*

Degree of Fever	Number of Children	Roentgenologic Condition: Normal	Roentgenologic Condition: Pneumonic Consolidation
None	154	116	38
Low	15	4	11
High	53	10	43

Even in the presence of high fever, roentgenograms of 10 children taken in the postero-anterior position showed no pulmonary abnormalities. Pulmonary consolidation was noted in the remaining 43 children (table 5). In this group 11 were mildly and 32 severely ill (table 3). Many of these children had clinical evidence of widespread pneumonic consolidation. Bronchial breathing could often be heard over both lungs, mainly at the bases, posteriorly. Roentgenologically, consolidation was noted 31 times at the base of the lung, 15 times in the hilar region and 11 times in the region of the upper lobes. The region of the cardiophrenic angle was involved in 15 of the 31 children who showed basal consolidation.

Roentgenograms were taken in the lateral position for 20 children of this group. In 11 of these, no abnormal changes were noted. Increased opacities in the region of the hilar lymph nodes were noted in only 1 child, and a homogeneous triangular shadow in the region of the middle lobe of the right lung was noted in 7 children (table 4).

COMMENT

Roentgenograms of the chest during an attack of pertussis, fourteen to twenty-one days after the onset of symptoms, often showed differences from the normal condition. The abnormalities most frequently found were increased pulmonary markings, homogeneous triangular shadows near the cardiophrenic angle and single or multiple opacities in any portion of the pulmonary field. In the lateral view involvement of the middle lobe of the right lung was often seen. The changes seen in the roentgenograms are inter-

preted as being due to pneumonic consolidation, atelectasis and mediastinal lymphadenitis.

An attempt was made by us to correlate the roentgen appearance of the chest with the clinical course of pertussis. Evidence of pulmonary involvement occurred whether the clinical course was mild, moderate or severe. However, among patients with pulmonary consolidation the percentage of persons who were moderately or severely ill was high (table 3).

Of the children who had no fever during their illness about one third showed increased pulmonary markings and about one fourth showed evidence of pulmonary consolidation. The incidence of pulmonary infiltration was much greater in patients who had fever (table 5). Pulmonary consolidation was found in 80 per cent of the children who had high fever. Seventy per cent of the children in this group were considered to be severely ill. Children who had low grade fever or normal temperatures were equally ill.

Roentgenograms frequently showed consolidation in the region of the right cardiophrenic angle. There was distortion of the shadow of the right cardiac border. When roentgenograms were made in a direct lateral position, a homogeneous triangular opacity was occasionally seen in the region of the middle lobe of the right lung. This shadow was usually but not always present when the posteroanterior views showed involvement of the cardiophrenic angle and was due, presumably, to atelectasis plus pneumonic consolidation of the lobe. Abnormal physical signs over this area were usually meager. The patient usually had fever when the roentgenogram showed a homogeneous shadow in the region of the middle lobe of the right lung.

We believe that the involvement of the middle lobe of the right lung is due to the nature of the secretion in pertussis and the structure of the bronchial tree. About three weeks after the onset of pertussis the bronchial tree contains a sticky, tenacious, viscous secretion. Older children, after a severe spasm, cough up tenacious plugs and seem relieved. Toomey [12] implanted Haemophilus pertussis on a special liquid medium, and the resultant growth adhered tenaciously to the walls of the culture flask. The bronchial tree has a number of subdivisions, studied by Kramer and Glass [13] and more recently and in greater detail by Adams and Davenport [14] and by Neil, Gwynne, Gilmour, Main and Fairclough.[15] A lobar bronchus breaks up into main segments supplying different parts of the lobe. On the right side the upper lobe has four main segmental branches, the middle lobe has two, an anterior (antromedial) and an axillary (posterolateral), and the lower lobe has four. Kramer [16] has stated the belief that the lobar bronchus to the middle lobe is really a segmental branch arising from the lower lobar bronchus. The caliber of the bronchial segment to the middle lobe corresponds to that of a second order bronchus and is smaller than that of the other lobar bronchi (fig. 3).

It is believed that the combination of tenacious mucus and a narrow lobar bronchus contribute to frequent atelectasis in the middle lobe of the right lung. This pulmonary condition is not

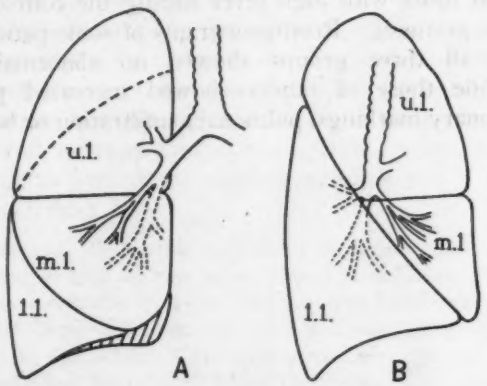

Fig. 3.—Diagrams of the right lung, showing position of the middle lobe and the lobar and main segmental branches of the bronchial tree. These diagrams show the middle lobe to be larger than it is usually represented. The lobar bronchus of the middle lobe is narrower than the lobar bronchus of the lower lobe. *A*, anterior view; *B*, lateral view. (Diagrams by Dr. Coleman Rabin.)

pathognomonic of pertussis but is present in other pulmonary infections [17] in which a thick, viscous, tenacious bronchial secretion is produced. Atelectasis of this lobe is occasionally found in measles.[6] It is perhaps more frequently seen in pertussis.

Roentgenograms from direct lateral exposure revealed that lymphadenopathy in the hilar regions was infrequent, whether the children had

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mild or severe infection. In our patients hilar enlargement was most frequent in those who showed no evidence of pulmonary consolidation, which confirms our postmortem observation that hilar adenopathy is infrequent. It had been believed by some that in most patients with pertussis there was enlargement of the tracheobronchial lymph nodes.

SUMMARY

Successive roentgenograms of the chest were made for 222 children between the ages of 5 months and 8 years during the course of pertussis. The roentgenograms were taken in the posteroanterior position and also, whenever possible, in the right direct lateral position.

The patients were divided into three groups: those with no fever, those with low grade fever and those with high fever during the course of the pertussis. Roentgenograms of some patients in all three groups showed no abnormality, while those of others showed increased pulmonary markings, pulmonary infiltration or both. Pulmonary involvement occurred in mild, moderate and severe illnesses. When fever was present, pulmonary consolidation and severe symptoms were more frequent. The most frequent site of pulmonary consolidation was the area of the cardiophrenic angle. Roentgenograms taken in the lateral position often revealed a homogeneous shadow in the area of the middle lobe of the right lung, interpreted as being due to atelectasis and pneumonic involvement. Later this area resumed its normal markings. Physical examination over the involved lobe gave little indication of abnormality. It is believed that the frequent involvement of the middle lobe of the right lung in pertussis may be due to the viscous nature of the secretion and the narrowness of the middle lobe bronchus.

Contrary to previous reports, roentgen evidence of enlarged tracheobronchial lymph nodes was infrequent. This confirmed the data derived from postmortem examinations.

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THE LEVINSON RATIO AND THE TRYPTOPHAN TEST

COMPARATIVE VALUE IN THE DIAGNOSIS OF TUBERCULOUS MENINGITIS

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AND JOHN A. TOOMEY, M.D.
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THE LEVINSON RATIO

In 1917 Tashiro and Levinson [1] described a test of the spinal fluid which was considered diagnostic for tuberculous meningitis. It was based on differential precipitation of the proteins of the spinal fluid by mercury bichloride and by sulfosalicylic acid, depending on the p_H of the fluid. The result of the test, known as the Levinson ratio, is considered positive if the amount of precipitate obtained by the action of mercury bichloride on the spinal fluid is at least twice as great as that obtained by the action of sulfosalicylic acid.

Several studies [2] made since that time indicate that the Levinson ratio is positive for 78 to 100 per cent of specimens of spinal fluid obtained from patients ill with tuberculous meningitis. Less agreement is to be found in the results from control tests of spinal fluids taken from normal persons and from patients ill with diseases other than tuberculous meningitis. Giordano and Abelson [2a] reported positive reactions for the spinal fluids of 26 per cent of patients ill with purulent meningitis, 33 per cent of patients ill with aseptic meningitis, 32 per cent of persons with miscellaneous conditions and 68 per cent of persons with syphilis of the central nervous system. Other workers obtained many false positive reactions, which they attributed to the presence of blood, pus or foreign serum in the spinal fluid.[3]

Since 1937 the Levinson test has been performed on samples of spinal fluid from 211 patients treated in the division of contagious diseases of City Hospital in Cleveland. Lumbar punctures were performed on the patients because of the possibility of some disease of the central nervous system, and all the tests were made as part of the routine examinations of the spinal fluid.

Method.—One cubic centimeter of spinal fluid was placed in each of two tubes, 8 mm. in diameter. One cubic centimeter of 1 per cent mercury bichloride was added to one tube and 1 cc. of 3 per cent sulfosalicylic acid to the other. The tubes were not disturbed for twenty-four hours, after which the levels of the precipitates were compared. The result was recorded as the ratio of the amount of precipitate in the tube containing the mercuric chloride to that in the tube containing the sulfosalicylic acid.

Results.—Of 211 patients, 36 had tuberculous meningitis, as proved by inoculation of guinea pigs, by autopsy or by both; all of the 36 died. The Levinson ratio was positive for 18 patients (50 per cent) and negative for 16 (44 per cent). For 2 patients who had more than one lumbar puncture the results were positive and negative at different times.

Of 77 patients with diseases of the central nervous system whose spinal fluids were clear, with low cell counts, the Levinson ratio was positive for 13 (17 per cent). Of 59 patients with purulent meningitis the Levinson ratio was positive for 9 (15 per cent), negative for 41 and positive and negative at different times for 9, the total number of positive reactions being 18 (30 per cent). Of 39 patients in whom there was no disease of the central nervous system the ratio was positive for 6 (15 per cent).

From the Division of Contagious Diseases, City Hospital, and the Department of Pediatrics, Western Reserve University.

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3. Gleich.[2b,c] Gleich and Weintraub.[2g]

THE TRYPTOPHAN TEST

Over the same period, since 1937, the test for tryptophan bodies was also performed on samples of spinal fluid from 166 patients with various diseases, a continuation of a study made by Toomey, Fulton and Rea in 1939.[4] At that time they reported a positive tryptophan reaction for less than 40 per cent of patients with tuberculous meningitis and for 23.8 per cent of persons with diseases other than tuberculous meningitis, thus confirming the results reported by Giustra[2e] but not those reported by Lichtenberg,[5] Baxter[6] and Spillane.[7]

Method.—Fifteen cubic centimeters of concentrated hydrochloric acid and 2 or 3 drops of a 2 per cent solution of formaldehyde were added to 3 cc. of spinal

Diseases and Reactions of Patients

	Levinson Ratio				Reaction to Tryptophan Test			
	Positive	Negative	Positive and Negative	Total No. of Patients	Positive	Negative	Positive and Negative	Total No. of Patients
Tuberculous meningitis	18	16	2	36	7	26	1	34
Diseases of the central nervous system with low spinal fluid cell counts								
Encephalitis	3	5	0	..	0	8	0	..
Poliomyelitis	8	36	0	..	0	36	0	..
Aseptic meningitis	1	0	0	..	0	1	0	..
Intracranial tumor	0	3	0	..	0	3	0	..
Syphilis of the central nervous system	0	2	0	..	0	1	0	..
Sinus thrombosis	1	2	0	..	0	1	0	..
Postpertussis encephalopathy	0	1	0	..	..	..	..	..
Toxic neuronitis	0	1	0	..	..	..	..	..
Tetanus	0	1	0	..	..	..	..	..
Intracranial hemorrhage	0	2	0	..	0	1	2	..
Embolus in brain	0	1	0	..	1	0	0	..
Bell's palsy	0	1	0	..	0	1	0	..
Multiple sclerosis	0	1	0	..	0	1	0	..
Tumor of the spinal cord	0	1	0	..	0	1	0	..
Peripheral neuritis	0	1	0	..	0	1	0	..
Myelitis	0	1	0	..	0	1	0	..
Congenital hydrocephalus	0	1	0	..	0	1	0	..
Hysteria	0	1	0	..	0	1	0	..
Cerebral thrombosis	0	2	0	..	0	1	0	..
Encephalopathy with nephritis	0	1	0	77	0	1	0	64
Diseases of the central nervous system with high spinal fluid cell counts								
Meningococcic meningitis	3	15	7	..	0	13	3	..
Influenzal meningitis	0	14	1	..	2	11	1	..
Pneumococcic meningitis	1	6	0	..	2	3	0	..
Streptococcic meningitis	3	5	1	..	1	5	1	..
Staphylococcic meningitis	0	1	0	..	0	1	0	..
Meningitis due to Meningococcus catarrhalis	1	0	0	..	0	1	0	..
Abscess (epidural and cerebral)	1	0	0	59	0	1	0	45
Other diseases with no changes in the spinal fluid								
Amytal poisoning	0	1	0	..	1	0	0	..
Pertussis	1	1	0	..	0	1	0	..
Miliary tuberculosis without meningitis (autopsy)	1	0	0	..	..	..	..	..
Acute rheumatic fever	0	2	0	..	0	1	0	..
Pyelitis	0	4	0	..	0	1	0	..
Tuberculosis in childhood	0	1	0	..	0	1	0	..
Upper respiratory infection	1	11	0	..	0	9	0	..
Streptococcic septicemia	0	1	0	..	..	..	..	..
Gastroenteritis	1	3	0	..	..	..	..	..
Furunculosis of external auditory canal	1	0	0	..	..	..	..	..
Pneumonia	1	3	0	..	0	2	0	..
Typhoid fever	0	2	0	..	..	..	..	..
Sinusitis	0	2	0	..	0	2	0	..
Syphilis	0	1	0	..	0	1	0	..
Scarlatina	0	1	0	39	0	1	0	20
No disease	..	..	..	..	0	3	0	3

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fluid. The solution was shaken, allowed to stand for a few minutes and layered with 2 cc. of 0.06 per cent sodium nitrite. The appearance of a delicate violet ring indicated the presence of tryptophan bodies.

Results.—The spinal fluids from 34 patients who had tuberculous meningitis, as proved by inoculation of guinea pigs, autopsy or both, were tested. The results were positive for 7 and negative for 26 of the patients. For 1 patient both positive and negative results were obtained. The total number of positive reactions therefore was 8.

Of 64 patients with diseases of the central nervous system, in whom the number of cells in the spinal fluid was low, there was only 1 whose spinal fluid gave a positive reaction; fluid from 2 others showed positive and negative reactions at different times. Of the spinal fluids from 45 patients with purulent meningitis 5 gave positive reactions (11 per cent) and 5 others reacted both positively and negatively at different times. Of 23 persons with miscellaneous diseases, without evidence in the spinal fluid of disease of the central nervous system, the reaction was positive for 1 (4 per cent).

To summarize, the reaction was positive for only 21 per cent of patients ill with tuberculous meningitis. However, it was also positive for 11 per cent of patients who were ill with diseases other than tuberculous meningitis.

CONCLUSION

1. More patients ill with tuberculous meningitis than with any other disease show a positive Levinson ratio and a positive reaction to the tryptophan test.

2. Neither test is of conclusive value in the diagnosis or exclusion of tuberculous meningitis.

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PROPHYLACTIC VALUE OF SULFATHIAZOLE AGAINST NEONATAL GONOCOCCIC CONJUNCTIVITIS

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There is still an appreciable incidence of neonatal gonococcic conjunctivitis in spite of legislation in forty-six of the United States requiring the instillation of silver compounds into the conjunctival sacs of every baby at birth.[1] From 1938 through 1942, 222 cases were reported in the city of New York[2] and 562 cases in the state of New Jersey.[3] The total number of cases reported from 1939 through 1943 in the city of New York in the municipal hospitals alone was 126.[4]

An investigation was carried out in the service for newborn infants at Harlem Hospital in order to prove the value of sulfathiazole in the prevention of gonococcic conjunctivitis. The routine instillation of silver nitrate into the conjunctival sacs of newborn infants was supplemented with the oral administration of sulfathiazole. Beginning Feb. 1, 1943, sulfathiazole was given orally, as a prophylactic, to all babies born in the hospital on odd days, while those born on even days received no drug and were used as controls. In both groups silver nitrate was instilled into the conjunctival sacs in the usual manner. Of the 2,687 babies born in the hospital during thirteen months, from Feb. 1, 1943 through Feb. 29, 1944, 1,425 were given sulfathiazole prophylactically, while 1,262 received no drug.

In a previous study[5] it was found that the average total dose of sulfathiazole required to cure gonococcic conjunctivitis in a newborn infant was 14 grains (0.91 Gm.), 3 grains (0.18 Gm.) as an initial dose and then 1 grain (0.06 Gm.) every four hours. Therefore, the same dosage was used prophylactically at the outset of the study. Three grains (0.18 Gm.) of the drug was given as an initial dose twelve hours after birth, with the first fluids given the infant orally, followed by 1 grain every four hours to a total of 14 grains. However, within the first two months of the investigation gonococcic conjunctivitis developed in 2 infants who were given sulfathiazole prophylactically. Therefore, the period of administration of the drug was extended to include a third day and the total dose was increased to 20 grains; 3 grains was given as an initial dose and then 1 grain was given every four hours to a total of 20 grains (1.2 Gm.). The accompanying table presents the results of the study.

Comparison of Incidence of Gonococcic Conjunctivitis in Newborn Infants Receiving Sulfathiazole Prophylactically and in Newborn Infants Not Receiving the Drug (February 1943 to February 1944, Inclusive)

	Number of Infants	Number with Gonococcic Conjunctivitis
Sulfathiazole given prophylactically	1,425	2
No drug given	1,262	6
Total	2,687	8

These statistics are significant. Gonococcic conjunctivitis occurred three times as frequently in the controls as in the infants given sulfathiazole prophylactically. Furthermore, the 2 infants in whom gonococcic conjunctivitis developed after they had received preventive treatment had been given only 14 grains of sulfathiazole over a period of two days. In eleven months after the total dose had been increased to 20 grains given over three days, gonococcic conjunctivitis did not develop in any infant. During the period covered by this study the control group showed an incidence of the disease comparable to that in previous years. In the previous four years (1939 through 1942) the incidence at Harlem Hospital was 13, 8, 13 and 7 cases. However, of the infants who were given sulfathiazole prophylactically, only 2 had gono-

From the Department of Pediatrics, Harlem Hospital.

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2. Rosenthal, T.: Personal communication to the authors.

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5. Blumberg, M. L., and Gleich, M.: The Simplified Treatment of Gonococcic Ophthalmia Neonatorum with Chemotherapy, J. A. M. A. **123:**132-134 (Sept. 18) 1943.

coccic conjunctivitis and these 2 infants probably received inadequate dosage.

All of the babies were observed carefully during the time they were in the hospital and in the follow-up clinic. No complications were noted in the infants who received sulfathiazole. The appetite, the character of the stools and the rate of gain in weight did not differ appreciably in the two groups. Routine urinalyses revealed no abnormal elements, such as red blood cells, pus cells, albumin or casts. None of the infants had sulfathiazole dermatitis or angioneurotic edema.

SUMMARY AND CONCLUSIONS

The incidence of neonatal gonococcic conjunctivitis is appreciable in spite of the fact that local instillation of silver preparations is compulsory in forty-six states.

Carefully controlled investigation for a period of thirteen months showed that effective protection against gonococcic conjunctivitis was afforded by oral administration of sulfathiazole in a total dose of 20 grains given over three days, starting twelve hours after birth.

As a result of this study, it is suggested that sulfathiazole be administered routinely by mouth for the prevention of neonatal gonococcic conjunctivitis as an adjunct to the existing prophylactic instillation of silver nitrate. This procedure would be of special value where medical attention is scarce and where, consequently, doctors either do not attend to deliveries or fail to follow up the health of the babies during the neonatal period. The use of sulfathiazole according to instructions left by the doctor, nurse or midwife who delivered each baby would help to eradicate neonatal gonococcic conjunctivitis.

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COMPARISON OF WESTERGREN AND KATO ERYTHROCYTE SEDIMENTATION RATE READINGS

RELATION TO THE CLINICAL STATUS OF CHILDREN WITH RHEUMATIC FEVER

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The erythrocyte sedimentation test is a laboratory procedure which may be of some help in diagnosing rheumatic fever and is known to be of definite aid in evaluating the clinical conditions of patients with this disease. During the acute and subacute or active phases of rheumatic fever it is common practice to obtain sedimentation values rather frequently to help in following the course of the disease. The most important use of the sedimentation values is as an aid in determining when the disease passes from the active to the inactive phase. After the infection has subsided, the physical activity of the patient can be increased safely. Clinically there is little need for taking frequent readings until the patient's general condition is such that there is a real question as to whether the disease is active or inactive. After the infection has subsided and the disease is inactive, it is common practice to obtain sedimentation readings as part of periodic examinations for evaluating the condition of the patient.

This study was undertaken to compare and confirm the normal ranges of the erythrocyte sedimentation rate as determined by a standard macroscopic and a standard microscopic method. Since there are several methods for determining the erythrocyte sedimentation rate, it is extremely important to know the normal range and the limitations of the method used. The Westergren macromethod and the Kato micromethod were compared as to their relative merits for hospital, sanatorial and clinical services.

In the hospital or sanatorium readings of sedimentation rate are made relatively frequently, and consequently the technician can become familiar with any reliable method, even though technically difficult. However, in field clinics infrequent determinations are needed, and the local technician can be expected to obtain reliable readings only if the method is technically simple.

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REVIEW OF LITERATURE

The literature on the phenomenon of erythrocyte sedimentation is extensive. Nichols [1] and Ham and Curtis [2] made interesting studies of data and opinions concerning some factors involved in the sedimentation test. Table 1 lists a number of methods of obtaining the sedimentation rate and the normal values reported for each. Haskins, Trotman, Osgood and Mathieu [3] found that the average sedimentation rate for 295 adults by Westergren's method was 4.5 mm. at forty-five minutes. Osgood and his associates,[4] using the Westergren method, have shown, with 261 subjects, that there were no differences in relation to age or sex in the sedimentation rates for children 4 to 18 years of age. They found that the rates formed a skewed curve, with the greater number of determinations falling in the lower ranges and a smoothed mean value of 10 mm. at forty-five minutes. They concluded that a value of 15 mm. at forty-five minutes, which was above the value of 80 per cent of the results, probably represented the upper limit of the normal range. Kato,[5] using his own method, reported a normal range for the

1. Nichols, R. E.: A Study of the Phenomenon of Erythrocyte Sedimentation, J. Lab. & Clin. Med. **27**: 1317 (July) 1942.

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5. Kato, K.: Use of Combination Microhemopipet, Am. J. Dis. Child. **59**:310 (Feb.) 1940.

sedimentation rate of 0 to 20 per cent at one hour. Benson and Rogers [6] reported sedimentation rates by the Cutler method for 327 healthy girls between 10 and 20 years of age. Ninety per cent of the values were between 2 and 13 mm. at one hour, and the normal was taken as 2 to 10 mm. at one hour. Landau [7] studied the relation between the reduced values obtained with his modification of the Linzenmeier-Raunert micromethod for the measurement of sedimentation and those obtained with the Westergren macromethod by performing simultaneous tests with the two methods on each of 300 patients. The yielded 985 pairs of determinations in the comparative study of the two methods. Values were also obtained for 8 healthy girls who were hospitalized for a long period for metabolic studies.

The sample of venous blood for the Westergren sedimentation method [8] was placed in a tube containing dry potassium oxalate, 2 mg. for each cubic centimeter of blood, and the tube was inverted several times for adequate mixing. The sample was then sent to the laboratory for analysis. After the blood had been mixed again, the sedimentation tube was filled and placed in a holder. The distance of fall of the erythrocyte column was recorded in millimeters at the end of forty-five minutes. The blood sample for the Kato micromethod [5] was obtained by puncturing a finger and was collected in a spot plate which had previously been oxalated by

TABLE 1.—*Methods of Measuring Erythrocyte Sedimentation Rate and Normal Values as Given by Various Authors*

Author	Method	Units of Measurement	Correction for Volume of Erythrocytes	Normal Values
Cutler, J.: Am. J. M. Sc. **171**: 882 (June) 1926	Distance of fall plotted for 1 hr. at 5 min. intervals	Slope of curve; mm. in 1 hr.	None	"Horizontal line": Men, 8 mm. in 1 hr.; women, 10 mm. in 1 hr.
Cutler, J.: Am. J. M. Sc. **173**: 687 (May) 1927	Micromethod, using capillary blood but otherwise the same as above			
Kato [5]	Micromethod, using capillary blood; distance of fall in 1 hr.	Percentage in 1 hr.	None	Normal range, 0 to 20% in 1 hr.
Landau [7]	Distance of fall after 1 hr.; original length of column of blood, 62.5 mm.*	Mm. in 1 hr.	None	Children under 2 yr., 1 to 6 mm. in 1 hr.; children over 2 yr., 1 to 9 mm. in 1 hr.
Rourke, M. D., and Ernstene, A. C.: J. Clin. Investigation **8**: 745 (June) 1930	Velocity of fall during the period of most rapid sedimentation	Mm. per min.	Required	0.08 to 0.35 mm. per min.
Smith, C. H.: Am. J. M. Sc. **192**: 73 (July) 1936	Micromethod, using capillary blood; distance of fall in ½ hr. and 1 hr.	Mm. in ½ hr. and 1 hr.	Hematocrit reading reported with the sedimentation rate	Infants and children, 1 to 8 mm. in ½ hr., mean 4 mm.; 3 to 13 mm. in 1 hr., mean 9 mm.
Walton, A. C. R.: J. Lab. & Clin. Med. **18**: 711 (April) 1933	Distance of fall in 1 hr.	Mm. in 1 hr.	Correction by graph	Men, 0 to 5.5 mm. in 1 hr., averaging 2.5 mm.; women, 0 to 5.5 mm. in 1 hr., averaging 3.5 mm.
Westergren [8]	Distance of fall in 45 min.	Mm. in 45 min.	None	Upper limits,† 15 mm. in 45 min.; mean, 10 mm. in 45 min.
Wintrobe, M. M., and Landsberg, J. W.: Am. J. M. Sc. **189**: 102 (Jan.) 1935	Distance of fall in 1 hr.	Mm. in 45 min.	Required	Upper limit, 10 mm. in 1 hr.

* Modification of Linzenmeier-Raunert method.
† Normal values based on work of Osgood et al.[4]

lower values proved to correspond fairly well, whereas the higher values showed greater differences.

METHOD OF STUDY

Samples of blood were taken periodically from children with rheumatic fever receiving sanatorial care, and readings were obtained by the Westergren and the Kato methods. Observations of the sedimentation rates were made over a period of two years. For the children in the sanatorium for persons with cardiac disease weekly determinations provided a survey of the progress of the patients for months at a time (charts 1 and 2). The group of 119 boys and girls 5 to 17 years of age

the addition of 0.2 to 0.3 cc. of 2 per cent potassium oxalate solution which was allowed to dry. Four or five drops of blood were placed on the spot plate and thoroughly oxalated by stirring with a thin glass rod. The micropipet was immediately filled, placed in a holder and set in a vertical position on the rack. The sedimentation rate was reported as the percentage of fall of the red cell column in one hour.

The common practice of obtaining samples of blood by venipuncture simplified the technic of the Westergren method. Values for the sedimentation rate were found to decrease when the samples of blood were allowed to stand. Table 2 shows the values obtained for 14 subjects when the samples of blood were tested at intervals after the venipuncture. The excessively high value of 114 (subject I) was not appreciably changed. In view of the changes shown by the other values, the error due to standing was most important when the sedimentation rate was near the upper limit of normal, 15

6. Benson, L., and Rogers, E. J.: The Blood Sedimentation Rate in Healthy Girls, J. Lab. & Clin. Med. **26**:987 (March) 1941.

7. Landau, A.: Microsedimentation (Linzenmeier-Raunert Method), Am. J. Dis. Child. **45**:691 (April) 1933.

8. Westergren, A.: Technique of Red Cell Sedimentation Reaction, Am. Rev. Tuberc. **14**:94 (July) 1926.

mm. in forty-five minutes. Consequently, determinations were started within a half-hour after the blood was drawn.

The collection of capillary blood received some attention. Freely flowing blood from a punctured finger is of course more easily obtained after the hand has been placed for several minutes in warm water. The sedimentation rates for 6 subjects were observed for possible variation when the temperature of the hand was changed. The patient's hands were placed in basins of water, iced and hot, for several minutes before the finger was punctured. The sedimentation rates then determined by the Kato method showed no appreciable variation.

	Kato Readings, % in 1 Hr.					
Subject	A	B	C	D	E	F
Temperature of the hand { Cold	44	20.5	20.5	20.5	3.5	13.5
Temperature of the hand { Warm	44.5	21	20	20	6	13

It was found that it is necessary for the technician to have had experience in obtaining freely flowing blood from a puncture of a finger and to be adept at following the procedure.

RESULTS AND COMMENT

The range of values for the 8 normal subjects by the Westergren method was 2 mm. to 28 mm. in forty-five minutes, and the mean value was 8.7 mm. These data are shown in table 3. This compares closely with the smoothed mean value of 10 mm. found by Osgood.[4] The range of values by the Kato method was 2.5 to 30 per cent, with a mean value of 10 per cent. This

TABLE 2.—*Effect of Allowing Blood to Stand Before Testing the Sedimentation Rate* *

Subjects	A	B	C	D	E	F	G	H	I	J	K	L	M	N
Before 30 min.	20.5	13	24	11	7	28	20	21	114.5	7	7	19	4	24
After 45 min.	19	12	16	10	4.5	22	12	..	.....	..	..	..	..	..
After 60 min.	..	..	..	..	..	..	..	17	114	7	6	17	2.5	22.5
After 90 min.	17	11	11	9	4	..	11.5	..	.....	..	..	..	..	..

* Westergren sedimentation rates: Millimeters in 45 minutes.

TABLE 3.—*Sedimentation Rates for Eight Normal Subjects*

Patient	C. A.		D. B.		B. G.		I. G.		V. R.		L. J.		I. L.		E. S.	
Age, yr.	12		14		12		11		14		11		13		11	
Method * ... Date	W	K	W	K	W	K	W	K	W	K	W	K	W	K	W	K
10/12/42	8	14	5	7	6	9	10	10	16.5	25	13	19.5	17	16	16.5	19.5
10/19/42	6	12	4.5	2.5	4.5	6.5	5	8	11.5	14.5	12	14	10.5	12	13	13
10/26/42	4.5	6.5	2.5	3.5	5	9	6	6	11	14.5	14	13	5	13	12	17.5
11/ 2/42	6	7	2.5	3.5	4.5	11	6	5	10.5	14.5	7	11	8	6	9	17
11/10/42	11	3	2	2.5	6	11	7	5.5	9	9.5	8	7	4	5.5	28	30
11/17/42	12	8	3	3	4.5	7.5	5	7	10	10.5	8	6.5	8	7	17	20
11/24/42	9.5	10.5	1.5	3.5	4	5	8	4	12	9	9	7	8.5	6.5	7.5	13
12/ 1/42	14	10	..	3	4	6.5	6	3	11	15	7	14	8	7	15	18

	Westergren	Kato
Range of values for the group	2 mm. to 28 mm.	2.5 to 30%
Mean values for the group	8.7 mm.	10%

* Method: W indicates Westergren values at the end of 45 min.; K indicates Kato values at the end of 60 min.

TABLE 4.—*The Mean Values of the Westergren Sedimentation Rate and the Kato Sedimentation Rate with Standard Deviations for Groups Classed According to the Kato and the Westergren Method Respectively*

Kato Sedimentation Rate, %	Equivalent in Terms of Westergren Method: Number of Subjects	Mean	Standard Deviation
70 to 74.5	1	....	....
65 to 69.5	7	104.0	6.0
60 to 64.5	9	88.5	15.3
55 to 59.5	24	78.7	16.1
50 to 54.5	22	74.8	20.8
45 to 49.5	30	55.5	15.8
40 to 44.5	63	50.2	23.0
35 to 39.5	64	32.6	15.0
30 to 34.5	108	30.4	18.9
25 to 29.5	125	21.9	11.5
20 to 24.5	136	17.5	8.8
15 to 19.5	147	13.5	7.4
10 to 14.5	88	11.8	8.0
5 to 9.5	79	9.6	8.3
0 to 4.5	87	10.2	10.5
Total	985	25.5	23.6

Westergren Sedimentation Rate, Mm.	Equivalent in Terms of Kato Method: Number of Subjects	Mean	Standard Deviation
105 and over	18	56.9	10.1
100 to 104.5	10	47.0	12.5
95 to 99.5	7	59.0	8.3
90 to 94.5	1	....	....
85 to 89.5	9	52.0	8.0
80 to 84.5	9	53.1	7.6
75 to 79.5	11	47.1	9.2
70 to 74.5	10	47.5	9.0
65 to 69.5	6	44.2	7.5
60 to 64.5	8	48.8	7.4
55 to 59.5	8	47.5	6.1
50 to 54.5	18	42.5	10.3
45 to 49.5	30	37.0	11.4
40 to 44.5	27	37.7	14.1
35 to 39.5	32	32.7	9.0
30 to 34.5	63	33.7	7.7
25 to 29.5	82	25.4	10.2
20 to 24.5	110	24.7	9.2
15 to 19.5	113	21.8	7.3
10 to 14.5	153	19.2	7.5
5 to 9.5	170	14.6	8.7
0 to 4.5	89	8.6	6.3
Total	985	24.9	14.7

range also was found to be in agreement with values given by Kato.[5]

Sedimentation rates for 119 children receiving sanatorial care were obtained by both methods. A comparative study was made of the 985 pairs of determinations obtained.

Table 4 was prepared to show the mean values of the Westergren sedimentation rate and the Kato sedimentation rate with standard deviations for groups classed according to the Kato and the Westergren method respectively. These data were comparable from the upper limits of normal to values of 30 to 40. Above this range the reliability of the Kato micromethod was limited, while the Westergren macromethod continued to record the sedimentation rates to a more accurate degree. The micromethod, however, showed the more progressive change in values within the range of 0 to 40. The coefficient of correlation between the two methods was 0.77.

The distribution of 412 Kato values for which the corresponding Westergren values were below 15 mm. at forty-five minutes was studied. Eighty per cent were 22.7 or less, 50 per cent were 15.4 or less and 30 per cent were 6 or less at sixty minutes. These values were in agreement with the normal ranges for the Westergren and Kato test, 1 to 15 mm. and 0 to 20 per cent respectively.

A chart was constructed for each subject, to show the relationship of the clinical and the laboratory findings (chart 1). The broken line curves in the center section represent the sedimentation rates. The solid line at 15, parallel to the base line, indicates the upper limit of normal for results obtained by the Westergren method.

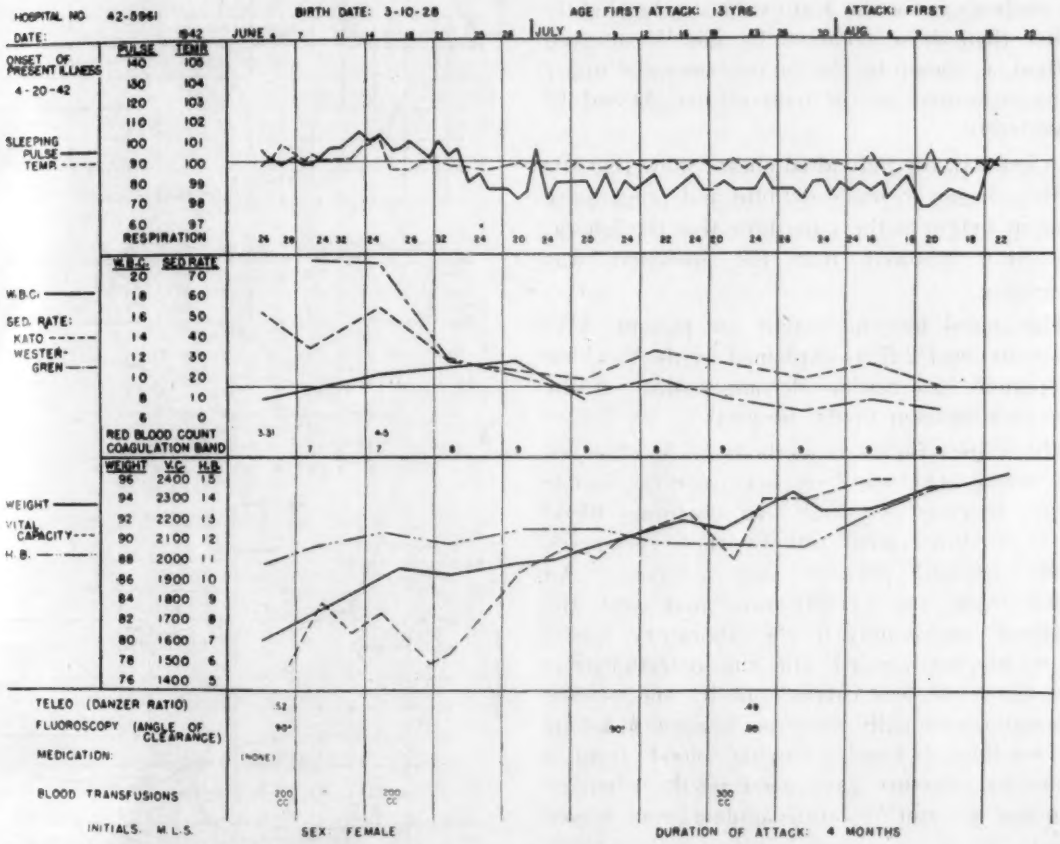

Chart 1.—This chart shows the changes in sedimentation rate for a patient with rheumatic fever during treatment and demonstrates the close correlation ordinarily observed between values obtained by the Westergren macromethod and by the Kato micromethod. The relationship of the sedimentation rates to other clinical and laboratory values is also shown.

Chart 2 shows the changes in the sedimentation rates of 4 children during treatment and demonstrates the close relationship ordinarily observed between values obtained by the Westergren macromethod and by the Kato micromethod. The charts also show the progress of the patients as to gain in weight and in vital capacity which accompanies the improvement, or decrease, of the sedimentation rate.

The wide difference in the elevated values in the active phase of rheumatic fever obtained

by the Westergren and the Kato methods causes one to realize the significance of interpretation. For example, patient CRT in chart *2 A* had a range of Westergren values from 120 to 10 and a range of Kato values from 60 to 19. The fact that the Westergren method gives a higher range of values indicates that it has greater sensitivity than the Kato method in evaluating the severity of the disease. In the upper ranges small changes in serial readings by the Kato method are, then, of greater significance than similar changes in readings by the Westergren method. As the decreasing sedimentation rates approach 30 the two methods become comparable. At this stage the tendency is for the Kato values to be slightly higher than those obtained by the Westergren method, as shown by the curves, since the upper limits of normal for the methods are 20 and 15 respectively.

In general, the individual charts show that the children began to make definite and progressive gains in weight at the same time that the laboratory tests showed that the infection was decreasing.

The initial loss in weight for patient AW, shown in chart *2 B,* is explained by the fact that the patient had cardiac decompensation at the time of admission to the hospital.

The values for both methods were observed and interpreted with respect to the possible technical errors involved. In obtaining blood for the sedimentation rate by the Westergren method several persons were involved. An intern made the venipuncture and sent the specimen immediately to the laboratory, where the technician carried out the determination. The Kato test was carried out by one person, although occasionally some one assisted in taking the readings. Freely flowing blood from a cutaneous puncture gave good results when an adequate amount of anticoagulant was mixed with it.

The importance of consistently exact technic was illustrated when a survey of the data revealed 28 inconsistent pairs of values. The two methods were evenly divided as to the number of values for sedimentation rates which were recognized as being too low. It was found that the discrepancies occurred in the months when vacations and changes in personnel took place. Questionable low values by the Westergren method indicated difficulty in making venipunctures, inadequate mixing of the blood and the anticoagulant or delay in starting the determination. Low Kato values similarly indicated possible faulty technic in obtaining and preparing the blood from a cutaneous puncture.

Other interesting values are shown in the following table.

Patient	Date	Kato	Westergren
V. E.	7/14	2	72
	7/21	3	71
	7/28	6	68
S. G.	4/ 7	21	110
	5/27	5.5	95

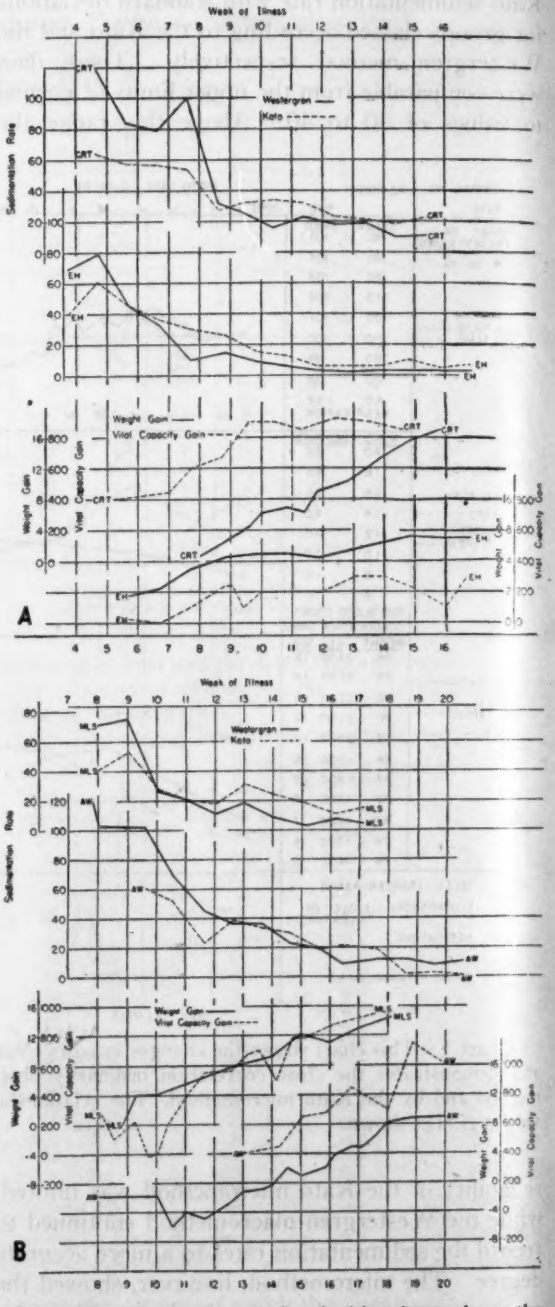

Chart 2.—Parts *A* and *B* of this chart show the changes in the sedimentation rates of 4 children during treatment and demonstrate the close relationship ordinarily observed between values obtained by the Westergren macromethod and by the Kato micromethod. The chart also shows the progress of the patients as to gains in weight and in vital capacity which accompany the improvement, or decrease, of the sedimentation rates.

The 2 subjects were severely ill and had poor peripheral circulation. Both subsequently died. Punctures of the fingers caused much distress on the part of the patients and difficulty for the technician. The Westergren values were high and in keeping with the clinical picture, while the Kato values were much too low. Consequently, in such circumstances the Westergren was the better method to use.

Although the coefficient of correlation of 0.77 indicated a high degree of relation between the two methods, as has been reported, there were fluctuations contrary to prediction for some individual records. A greater degree of correlation would have been found if the data subject to the errors noted in the preceding paragraphs had been excluded. Generally, the Kato values were higher within the limits of the normal range, while the Westergren values were higher in the range above 30 or 40.

SUMMARY AND CONCLUSIONS

The range of values for sedimentation rates of 8 healthy girls determined by the Westergren method and by the Kato method compared favorably with values found in the literature. The Westergren values ranged from 2 to 28 mm. in forty-five minutes, giving a mean value of 8.7. The Kato values ranged from 2.5 to 30 per cent in sixty minutes, with a mean value of 10 per cent, as shown in table 3.

The 985 pairs of sedimentation rates obtained by the two methods for 119 children receiving sanatorial care were compared, as shown in table 4. These data were comparable from the upper limits of normal to values of 30 to 40. The Westergren values, having a higher range than the Kato values, showed greater sensitivity in evaluating the severity of the disease. The Kato method showed a more progressive change in values from 0 to 40. However, the coefficient of correlation, 0.77, indicated a high degree of relation between the two methods.

A study of the distribution of 412 Kato values for which the corresponding Westergren values were below 15 mm. at forty-five minutes revealed that 80 per cent were 22.7 or less, 50 per cent were 15.4 or less and 30 per cent were 6 or less at sixty minutes. These values were in agreement with the normal ranges for the Westergren and the Kato test, 1 to 15 mm. and 0 to 20 per cent respectively.

It was found that a strict routine was necessary in the technic for either method, as errors could easily be made. As the drawing of blood by venipuncture is one of the most common technics used by doctors and by technicians, the Westergren method was less complicated than the Kato method. It was found necessary to send the venous blood to the laboratory immediately, as values tended to approach the normal if the sample was permitted to stand for more than a half-hour. The Kato method, using freely flowing capillary blood from a puncture of the finger proved to be more difficult for the inexperienced technician.

The erythrocyte sedimentation test proved to be of definite value in the evaluation of the clinical condition of patients with rheumatic fever. Values obtained by either method followed closely the clinical course of the patient with rheumatic fever. The micromethod, avoiding venipuncture, was more convenient when the determinations were made by an experienced technician. However, the macromethod can safely be done by a less experienced technician if a few precautions are taken. During the acute phase of the disease the macromethod was more sensitive, giving higher values than the micromethod. When the patient is extremely ill values obtained by the micromethod may be entirely unreliable.

Physicians should realize that there are a number of methods for determining the erythrocyte sedimentation rate and that it is necessary to know the normal range and limitations of the method they elect to use. Technical errors can be made easily, regardless of the method. In deciding when rheumatic fever has become inactive it is desirable to correlate all the clinical and laboratory findings and not to place too much emphasis on any one clinical or laboratory test.

Children's Hospital.

Case Reports

EPIPHYSIAL DYSGENESIS ASSOCIATED WITH CRETINISM IN A PREMATURE INFANT

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CHICAGO

In 1927 Fairbank [1] described "stippled epiphyses" associated with dwarfism, but he failed to recognize thyroid deficiency as the basis of the disturbance. Ten years later (1937) Reilly and Smythe [2] described 5 similar cases, designating the condition as "cretinoid epiphysial dysgenesis." McCullough and Sutherland [3] in 1940 described stippled epiphyses in a dwarf in whom there was no sign of hypothyroidism and used the term "epiphysial dysplasia puncticularis" to designate the skeletal change. The patient was not given thyroid, but McCullough and Sutherland stated that he increased in stature when treated with calcium, vitamin D and androgen. Wilkins,[4] who found bilateral epiphysial dysgenesis in 23 of 25 children with hypothyroidism, said that he had never seen true dysgenesis in any type of dwarfism other than that occurring with hypothyroidism. In his extensive review of the subject he cited reports of 36 cases observed by Läwen,[5] Roth,[6] von Seemen [7] and Looser.[8]

In roentgenograms epiphysial dysgenesis is diagnosed by the appearance of multiple small irregular islets of calcification, scattered over a considerable area. The islets are irregularly spaced, and the anatomic distribution does not conform to that of the normal centers of ossification. As the islets grow larger or new ones occur, they appear to coalesce and give the impression of a single large center which has undergone fragmentation. The defect is apparently due to an abnormality of endochondral ossification.

From Cook County Hospital.

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REPORT OF A CASE

A boy with epiphysial dysgenesis associated with cretinism was born at Cook County Hospital on Sept. 3, 1941. The mother, a tall, thin 35 year old woman of Swedish descent, was an unmarried primipara. She received no antepartum care and she stated that except for severe vomiting in the first trimester her pregnancy was normal and that delivery was at term. On August 27, six days before delivery, she presented herself at the Cook County Hospital Prenatal Clinic and was hospitalized because of hypertension. The Wassermann reaction of her blood was negative; her blood contained 233 mg. of cholesterol per hundred cubic centimeters of plasma (normal, 165 to 200 mg.). The delivery was normal.

The mother's family history revealed no instance of disease of the thyroid gland or of congenital defect. The infant's maternal grandmother was small in stature but was otherwise normal. The infant's father was a well built man of about 5 feet 8 inches (173 cm.).

The baby (fig. 1) weighed 4 pounds and ½ ounce (1,800 Gm.) at birth, and the recorded length was 15½ inches (39 cm.). Aspiration with a tracheal catheter was required before regular respiration was established. The cry was moderately strong. Except on the feet, which were slightly cyanotic, the infant's skin was pink. The head was square; the frontal and parietal bosses were prominent, and the vertex was extremely flat. A prominent epicanthal fold caused the widely separated eyes to appear slanting. The nose was flat, devoid of a bridge and almost flush with the face. The mandible was square, forming almost a straight line from the angle of the ramus across the chin. The mouth was extremely wide, and the thick, purple tongue protruded beyond the lips. The neck was so short that the head appeared to rest on the shoulders. The chest was barrel shaped. The lungs were clear; the heart was apparently normal, and no murmur was heard. The abdomen was soft, and the spleen was palpable. The genitalia were normal; both testicles were in the scrotum. The second toes overlapped the third toes on both feet, and the fingers were somewhat rigidly hyperextended, but there was no hyperflexibility of the extremities. The Moro reflex was present and normal.

Measurements taken the day after birth (September 4) were as follows: length, 36.3 cm.; sitting height,

23.3 cm.; cranial circumference, 32.0 cm., and thoracic circumference, 26.4 cm.

At this time diagnoses considered were cretinism, chondrodystrophy, hypertelorism and mongolism.

The laboratory data follow:

Blood Counts:

Date	Hemoglobin, Mg./100 Cc.	Erythrocytes, No./Cu. Mm.	Color Index	Leukocytes, No./Cu. Mm.	Polymorphonuclear Leukocytes, %	Lymphocytes, %	Eosinophils, %	Monocytes, %
10/17/41	11	3,220,000	1.00	4,720	56	35	1	7
10/28/41	13	3,510,000	1.11	12,300	44	52	1	3
11/ 4/41	11	3,620,000	0.91	10,050	27	71	0	2
11/ 8/41	12	3,410,000	1.05	14,050	58	37	0	5

Blood Chemistry:

Date	Cholesterol, Mg./100 Cc.	Calcium, Mg./100 Cc.	Phosphorus, Mg./100 Cc.	Phosphatase, Mg./100 Cc.
9/22/41	143	....	....	.....
9/30/41	119	....	....	.....
10/27/41	...	8.84	3.71	16.69
11/18/41	121	9.60	4.35	.....
Mother's Blood:				
9/13/41	232	9.90	4.27	5.67

The urine, examined on Sept. 13, 1941 and every week thereafter, was completely normal.

The blood gave a negative reaction to the Wassermann test on September 19 and October 27.

A twenty-four hour specimen of urine, 90 cc., contained 19 mg. of creatinine and 3 mg. of creatine (as creatinine), 22 mg. of total creatinine. The coefficient for preformed creatinine was 11.2; for creatine, 1.7, and for total creatinine, 12.9.[9]

Roentgenologic studies of the long bones on Sept. 13, 1941 (fig. 2*A*) showed multiple punctate calcified foci in all the epiphysial centers. This condition was most apparent in the lower femoral epiphyses and in the cuboid bones (fig. 2*B*); however, foci were scattered throughout all the epiphyses, including those of the vertebral spines (figs. 3 and 4). The roentgenologic diagnosis was epiphysial dysgenesis.

The infant was extremely hungry. He began each meal with gusto but would often become cyanotic during feedings and would tire quickly. There seemed to be severe mechanical difficulty in swallowing, due to the large, thick tongue and to incoordination. The medicine dropper containing his food had to be placed far back in the mouth, almost into the pharynx, and exceedingly small amounts of food were given at a time.

On October 11, when the infant was approximately 5 weeks of age, fever developed (axillary temperature, 101 F.), accompanied with rapid respiration and moist rales throughout both lungs. The bronchopneumonia responded to treatment with sulfathiazole and cleared entirely in eight days. On October 13, two days later, a loud systolic murmur was heard, for the first time, over the entire precordium. The heart was enlarged to the right and to the left, and the liver was palpable 3 fingerbreadths below the right costal margin.

After all the laboratory data had been collected and the infant had recovered from bronchopneumonia, thyroid therapy was instituted. On October 26, when the infant was approximately 7 weeks old, thyroxin was exhibited in doses of 0.2 mg. every five days (equivalent to 1/10 grain [0.006 Gm.] of thyroid daily). After receiving thyroxin the infant ate better and gained weight. By November 11 the weight had increased from 3 pounds 6 ounces (1,480 Gm.) to 3 pounds 10 ounces (1,600 Gm.). On this date the dosage of thyroxin was increased to 0.2 mg. three times weekly. On November 17, after a total of

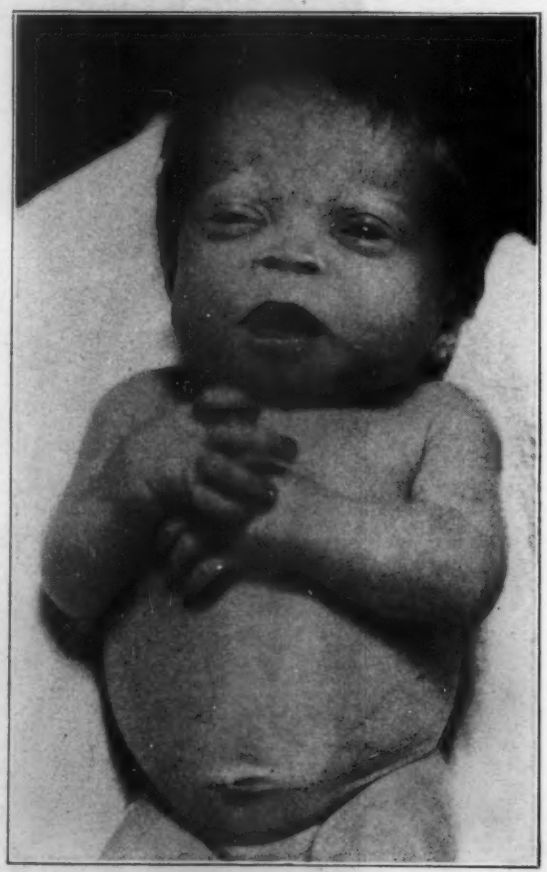

Fig. 1.—Photograph of a premature infant with cretinism, showing the characteristic appearance.

1.6 mg. of thyroxin had been given, the medication was stopped, because, with a rise in temperature, physical signs of bronchopneumonia developed. The infant was again given sulfathiazole, and, although the chest cleared, he fed poorly and went downhill until the time of his death, Dec. 1, 1941.

The clinical diagnosis was cretinism and prematurity. The postmortem observations were as follows:

The body was that of a poorly nourished white infant boy. There was extreme flattening of the nose. The frontal bosses were prominent, and both fontanels were widely patent. The crown-pubis measurement was 26 cm.; the pubis-heel measurement, 13.5 cm.; the distance from the midsternum to the end of the radius, 15 cm.; the

9. Excretion of creatinine and especially of creatine by this infant was greatly increased as compared with the values obtained for premature but otherwise normal infants by Marples and Levine (Am. J. Dis. Child. **51**:30 [Jan.] 1936).

cranial circumference, 33 cm.; the occipitofrontal diameter, 12 cm., and the biparietal diameter, 9.5 cm.

The pupils were mid-dilated, round and equal, and the conjunctivas were purple-tan. The tongue was large and thick and protruded from the mouth. The lower jaw was unusually prominent and formed a straight line with the nose and forehead. The finger and toe nails were long, and the nail beds were pale. The neck was short, and there was obvious wasting of the entire body. The ribs flared, and the abdomen had the appearance of a "pot-belly." The left testicle was in the upper part of the scrotum; the right testicle was fully descended.

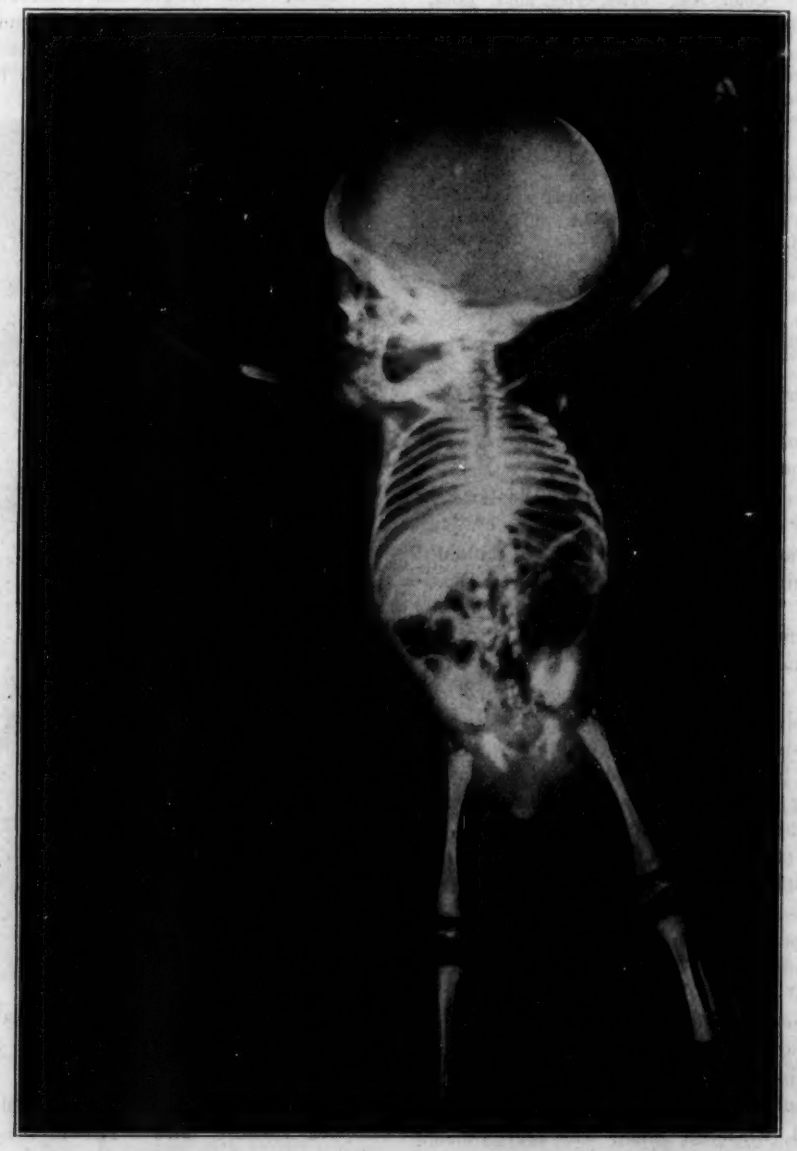

Fig. 2.—Roentgenograms of infant with epiphysial dysgenesis associated with cretinism showing the generalized distribution of stippled, calcified foci.

The pleura and the pericardial sac were free. The diaphragm was at the third intercostal space on both sides. The thymus gland was rudimentary.

The heart weighed 9 Gm. The myocardium was pale pink-tan and moderately firm. The chambers were slightly dilated. The left ventricle measured 6 mm.; the right, 3 mm.; the pulmonary artery, 23 mm., and the aorta, 18 mm. The valvular leaflets were unchanged. The ductus arteriosus was widely patent, and the foramen ovale had a 2 mm. defect, but the septum between the ventricles was intact.

The midline fat of the abdominal wall was absent. The lower border of the liver was at the xiphoid process and at the right costal margin. The lower pole of the spleen was at the eighth rib, in the posterior axillary line. The stomach and the colon were dilated with gas. The peritoneum was free, and the cecum and the ascending colon had a free mesentery.

The left lung was subcrepitant, and on section the lobes were pink-tan and slightly moist with blood. The right lung, which consisted of two lobes, was subcrepitant to crepitant. The pleura was smooth and blue-gray posteriorly. On section the lobes showed a

large, confluent, somewhat bloody area of dark purple-red in the posterior aspect. The bronchi were free and pink-tan, and the lymph nodes were small. Microscopically it was seen that most of the alveoli of the lungs were filled with polymorphonuclear leukocytes and erythrocytes, the interstitial blood vessels were dilated and congested and the bronchi were collapsed and contained a few inflammatory cells.

The mucosa of the stomach was smooth and light tan. The pylorus was slightly thickened.

The spleen weighed 6 Gm. It was firm, and the capsule was thin. On section the surface was red and the markings could not be made out. Microscopic examination of the spleen showed congestion of the sinusoids and slight increase of the interstitial fibrous connective tissue.

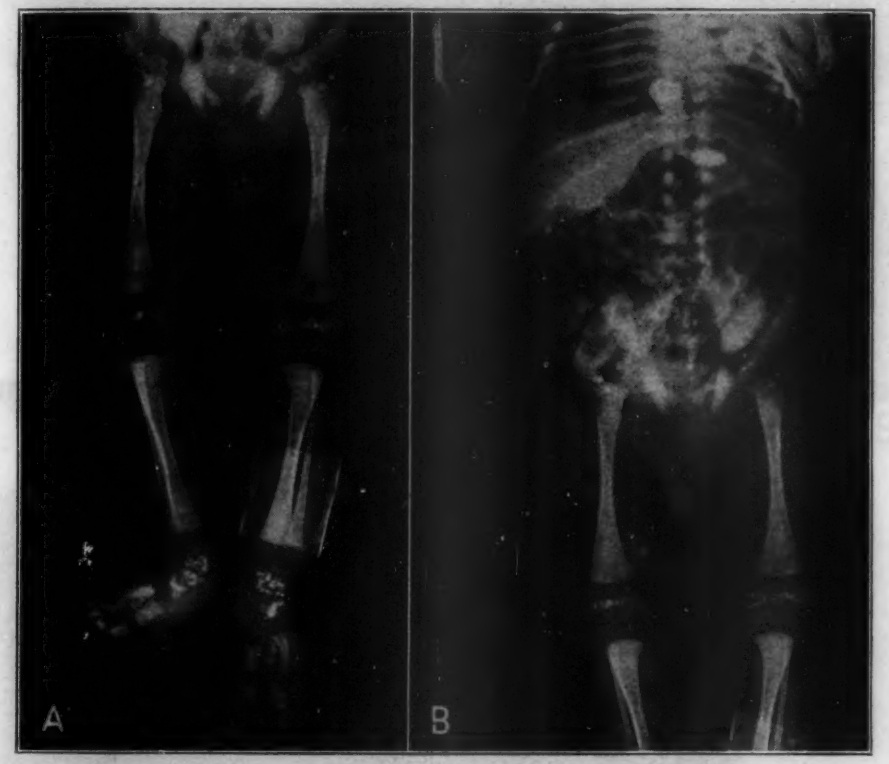

Fig. 3.—Roentgenograms of infant with epiphysial dysgenesis associated with cretinism showing *A*, epiphysial dysgenesis of both femoral epiphyses and of the cuboid bone and *B*, multiple stippled foci along the vertebral column.

The liver weighed 55 Gm. The consistency was less firm than usual, and the capsule was soft, thin and smooth. On section the surface was tan-brown and the lobular markings were distinct. Microscopically, the hepatic cells were seen to be granular and swollen, compressing the adjacent sinusoids. Scattered throughout were single hepatic cells and confluent areas of hepatic cells showing hydropic degeneration. The portal triad was unchanged. The gallbladder contained 1 to 2 cc. of bile; the wall was thin and the mucosa smooth.

The pancreas weighed 2.5 Gm. The consistency was moderately firm. On section the surface was light tan and the lobulations were indistinct. Microscopic examination revealed moderate to extreme increase of interstitial fibrous tissue, separating the acini and causing partial atrophy of the cells. The islands of Langerhans were moderately large, pale staining and cellular.

The mucosa of the small and large intestine was light tan, and the intestines contained lumps of hardened, bright yellow feces.

The adrenal glands weighed 4 Gm. The cortex measured 1 mm. and was light yellow; the medulla was soft and red-brown. Examined microscopically the adrenal glands showed normal distribution of cortical cells; the individual cells contained much lipid material. Neuroglia cells were present in the medulla. The capsule was moderately thickened and fibrotic, and the interstitial blood vessels were congested.

The two kidneys together weighed 18 Gm. The consistency was firm, and on section the capsule could be stripped with ease, leaving a smooth, shiny surface which showed fetal lobulation. The cortex measured 2.5 cm. and was light pink-tan; the medulla was dark red-tan. The cortical markings could barely be made out. Microscopic examination revealed cloudy swelling of the tubular epithelium and passive congestion of the interstitial blood vessels and of the capillaries of the glomeruli.

The prostate gland was uniform yellow-gray.

The testicles each measured 0.8 cm. by 0.5 cm. On section they were yellow-brown. Microscopically, the tubules appeared cellular and showed evidence of spermatogenesis and in places increased fibrous connective tissue separated the tubules. The capsule was thickened and fibrotic. The epididymis contained large tubules lined by columnar epithelium and surrounded by fibrous tissue.

The brain showed some postmortem softening. The meninges were thin and translucent.

The bones of the calvarium seemed more calcified and firm than usual. The epiphysial plates of the femurs seemed unchanged, extremely thin and regular. The epiphysial cartilage contained foci of calcification which grated under a knife and clicked when tapped with a metal instrument. These calcified areas were opaque and gray-white. Microscopic examination revealed that the periosteum was thickened and fibrotic. The bony trabeculae stained bluish pink and were only partially calcified, and a few cartilage cells remained in the bony spicules. The bone marrow contained erythropoietic and myelopoietic elements and numerous megakaryocytes. The cartilaginous trabeculae in the epiphyses were unchanged and regular, but within the cartilaginous tissue of the epiphyses were focal areas of calcification and isolated areas of fibrous connective tissue. In focal areas the cartilage cells were arranged in trabecular form.

Microscopic examination of the thyroid gland showed large and small alveoli lined with low columnar epithelium and filled with light pink, homogeneous colloid material. An increased amount of fibrous connective tissue separated the follicles, and the interstitial blood vessels were congested.

COMMENT

Roentgenologically, epiphysial dysgenesis may be confused with osteochondritis deformans. However, the latter usually occurs in epiphyses which previously have appeared normal on roentgen examination. Furthermore, osteochondritis deformans (Legg-Calvé Perthe's disease, Osgood-Schlatter disease) is usually unilateral, occurring most frequently in only one epiphysis. It is generally accompanied by pain and does not respond to thyroid therapy.

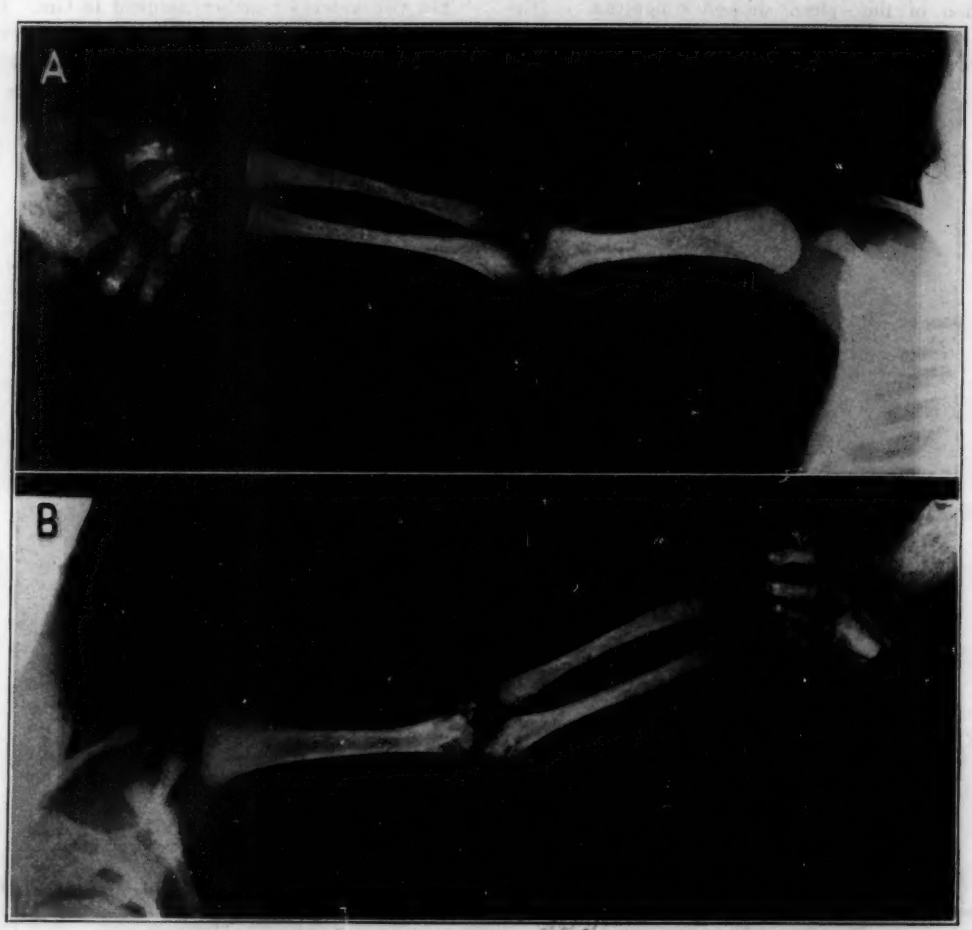

Fig. 4.—Roentgenograms of *A*, right arm and *B*, left arm of infant with epiphysial dysgenesis showing multiple calcified foci at the lower ends of the humeri and in the metacarpal bones.

Achondroplasia fetalis may be confused with cretinism clinically, but the latter may be differentiated by the unique deformities of the metaphyses and shafts of the long bones and the grossly abnormal shapes of the epiphyses.

Dr. H. G. Poncher and Mrs. G. Ricewasser, Chemist, both of the College of Medicine, University of Illinois, provided these data.

185 North Wabash Avenue.

Cook County Hospital.

PNEUMOCOCCIC MENINGITIS

COMPLETE RECOVERY OF A SIX MONTH OLD INFANT TREATED WITH PENICILLIN

ABRAHAM M. LITVAK, M.D.; EMANUEL APPELBAUM, M.D., AND MORTON GREENE, M.D.

BROOKLYN

Prior to the introduction of the sulfonamide compounds pneumococcic meningitis was almost invariably fatal. With the advent of these drugs, particularly sulfapyridine and sulfadiazine, the prognosis for patients with meningitis of this type was considerably improved. The introduction of penicillin marked another advance in the treatment of this disease. However, the number of reported recoveries from pneumococcic meningitis following penicillin therapy has up to the present time remained small. It has therefore seemed worth while to place on record our case, in which a dramatic recovery followed the use of this new drug.

REPORT OF A CASE

L. R., a 6 month old boy, was admitted to Beth-El Hospital on Nov. 1, 1943, in a state of generalized convulsions. The history revealed that the infant had been fretful and listless and had shown disinclination for food for forty-eight hours prior to admission to the hospital. Examination by the family physician before admission revealed an injected pharynx and a temperature of 102.6 F. Sulfadiazine was prescribed, but after the first dose of the drug a generalized convulsion supervened, lasting thirty or forty minutes. Sulfadiazine therapy was discontinued. The infant's condition remained stationary for the next twenty-four hours. However, the convulsions recurred the next morning, and the infant was brought to the emergency room of the hospital.

The history of the birth, feeding and physical and mental development of the infant have no bearing on the present illness.

Examination on admission revealed a well developed, well nourished infant in a state of generalized convulsions. Respiration was stertorous and irregular; the patient was cyanotic, and his temperature was 101 F. He appeared moribund. The anterior fontanel was tense and bulging; the neck was not resistant to anterior flexion; the pupils were dilated, divergent and fixed, and there was a vacant stare. The left ear drum revealed mild catarrhal otitis media, and the pharynx was injected. Examination of the chest revealed normal resonance over both lungs, with normal breath sounds. The heart was normal. The abdomen was soft; the liver and spleen were not palpable; no masses were felt in the abdominal cavity, and there were no cutaneous rashes. Neurologic examination revealed the absence of nuchal rigidity; Kernig's and Brudzinski's signs were

Table of Data for Studies of Spinal Fluid

Date	Color	Number of Cells	Type of Cells, %		Sugar, Mg. per 100 Cc.	Protein, Mg. per 100 Cc.	Chloride, Mg. per 100 Cc.	Smear	Culture
			Polymorphonuclear Leukocytes	Lymphocytes					
11/ 1/43	Turbid	886	98	2	0	135	694	Pneumococci abundant	Positive for pneumococci type 19
11/ 2/43	Turbid	450	98	2	0	...	...	Beginning clumping and phagocytosis of pneumococci	Negative
11/ 3/43	Turbid	440	60	40	66	...	...	Further clumping and phagocytosis of pneumococci	Negative
11/ 4/43	Turbid	200	80	20	68	...	...	Extensive clumping and phagocytosis of pneumococci plus disintegration	Negative
11/ 5/43	Ground glass	275	80	20	71	...	...	Morphology and staining of pneumococci impaired	Negative
11/ 6/43	Ground glass	275	75	25	66	...	...	Debris of pneumococci	Negative
11/ 7/43	Ground glass	...	..	..	..	...	...	Negative	Negative
11/ 8/43	Clear	66	80	20	70	75	742	Negative	Negative
11/ 9/43	Clear	110	80	20	73	70	742	Negative	Negative
11/10/43	Clear	50	50	50	..	..	...	Negative	Negative
11/11/43	Clear	40	60	40	73	..	...	Negative	Negative

From the Pediatric Service of Abraham M. Litvak, M.D., Beth-El Hospital.

not elicited; Chvostek's and Trousseau's signs were not present, and there was no carpopedal spasm. The right arm and right leg were spastic, and the Babinski sign was elicited bilaterally.

Sodium bromide was given rectally to control the convulsions, and oxygen was administered for the first three hours after the patient was admitted to the hospital. A lumbar puncture was performed, and cloudy fluid under pressure was obtained.

Two grams of sodium sulfadiazine in 200 cc. of distilled water was administered intravenously, followed by 250 cc. of 5 per cent dextrose in isotonic solution of sodium chloride. In the meantime the laboratory reported that the spinal fluid contained no sugar but many polymorphonuclear leukocytes and gram-positive cocci identified as pneumococci type 19 (table). The temperature had risen to 103.4 F. The infant was in a state of stupor, and his condition appeared critical. It was at this time that penicillin therapy was decided on.

In accordance with instructions received from Dr. C. S. Keefer 5,000 Oxford units of penicillin was given intrathecally twice a day and 2,500 units intramuscularly every three hours. Otologic examination revealed some bulging of the left ear drum, and myringotomy yielded a sanginueous fluid in which no pneumococci were demonstrated on culture. Cultures of blood and of material from the throat were negative for pneumococci.

On November 3 the infant's temperature rose to 106 F. Nuchal rigidity and generalized spasticity became more evident. Positive Babinski, Kernig and Brudzinski signs were elicited. The anterior fontanel was still tense and bulging. Despite the apparent improvement of the cerebrospinal fluid as judged by the laboratory reports, the clinical condition of the patient was worse than at any previous time. He was in a semistuporous state and had a vacant stare; there was no reaction to light or external stimuli. The prognosis for recovery appeared doubtful at this time. In view of the grave condition of the child the dosage of penicillin was doubled, so that 20,000 units was given intraspinally once daily and 5,000 units intramuscularly every three hours (chart).

On November 4 paralysis of the right facial nerve became manifest. Roentgen examination of the chest revealed the presence of a bronchopneumonic process, although clinically the lungs were normal.

On November 5 the general condition of the child appeared somewhat improved. The vacant stare and the fright that was evident when the crib was jarred were diminished. The anterior fontanel was not bulging, and the nuchal rigidity was diminished. The temperature, which had slowly but progressively declined after the third day, was now 100.5 F.

On November 7 the infant's condition was greatly improved; he responded to stimuli in a normal manner. The vacant stare disappeared completely, and the pupils were equal and reacted to light, although the eyes did not follow light. No paralysis was in evidence, and the Kernig and Brudzinski signs were absent. The ears and the eyegrounds at this date were normal. The dosage of penicillin was now reduced to 2,500 units intramuscularly every three hours and 10,000 units intraspinally once daily.

Clinical improvement progressed so rapidly that by November 11 the condition of the infant appeared satisfactory. The temperature was normal, and there were no meningeal signs, such as hypertonicity, bulging of the fontanel or separation of the sutures. Daily measurement of the head showed that it had not increased in size. The child behaved normally in every way. In view of the clinical condition and laboratory findings at this date (table and chart) penicillin therapy was discontinued. As indicated in the chart, the total amount of penicillin used was 480,000 units.

Supportive therapy consisting of small transfusions (150 cc.) of blood and saline clyses was given during the course of the illness.

Five days after the temperature had returned to normal, four days after the cessation of penicillin therapy, the patient was discharged completely recovered.

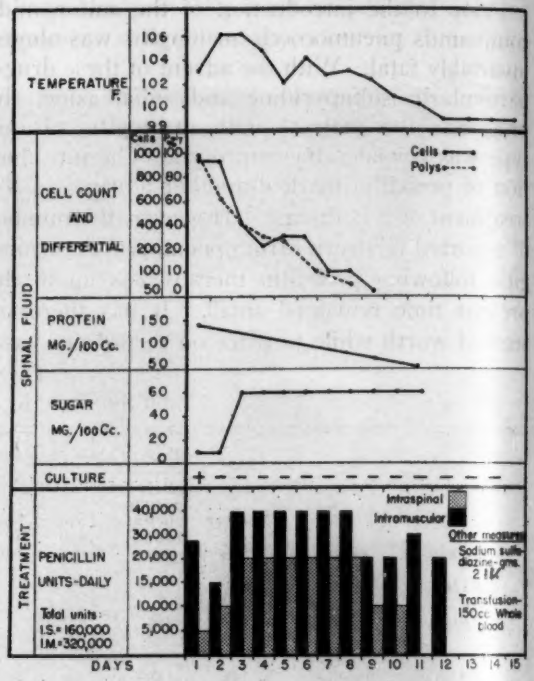

Chart of clinical and laboratory data for patient with pneumococcic meningitis treated with penicillin.

Follow-up study three and a half months after discharge from the hospital showed an apparently healthy child without any residual changes. The neurologic examination revealed no abnormality, and the measurements of the head were normal. The infant's behavior was normal in every respect.

COMMENT

The response of a nearly moribund infant to penicillin was little short of astounding. While the improvement was not immediate, once it began it progressed rapidly. It is also important to note the rapid improvement in the spinal fluid. Cultures of the spinal fluid were sterile after the first day of penicillin therapy. In addition, the drug caused early clumping and phagocytosis of pneumococci. This phenomenon was progressive and was associated with changes in the morphology and the staining qualities of the organisms. It is extremely unlikely that the small amount of sulfadiazine administered had any contributory effect.

1145 Eastern Parkway.

Abstracts from Current Literature

Biochemistry; Bacteriology, and Pathology

ISOLATION OF NEISSERIA FLAVA FROM THE GENITOURINARY TRACT OF THREE PATIENTS. CHARLES M. CARPENTER, Am. J. Pub. Health **33**:135 (Feb.) 1943.

During an epidemiologic investigation of gonococcic infections Neisseria flava was isolated from 3 of 505 patients. All 3, a 37 year old married Negress, a 17 year old single Negress and a 41 year old married white man, presented symptoms similar to those of gonococcic infections. From none of them was Neisseria gonorrhoeae observed in either films or cultures. After treatment with sulfathiazole neither organism could be demonstrated.

The biologic characteristics of the three strains isolated were similar. Discrete, opaque, pale yellow colonies, slightly flatter than those of the meningococcus, were formed on chocolate blood agar. Dextrose, maltose and levulose were fermented. Morphologically the organisms resembled the meningococcus more than the gonococcus.

N. flava is considered to be part of the normal flora of the upper respiratory tract. This is the first report of the isolation of this type of N. flava from the human genitourinary tract.

PLATT, Gouverneur, N. Y.

CHANGES IN THE BACTERIAL CELL BROUGHT ABOUT BY THE ACTION OF GERMICIDES AND ANTIBACTERIAL SUBSTANCES AS DEMONSTRATED BY THE ELECTRON MICROSCOPE. STUART MUDD, Am. J. Pub. Health 33:167 (Feb.) 1943.

The author describes the changes visible under the electron microscope following (1) the exposure of bacteria to the simple salts of heavy metals, (2) the exposure of Eberthella typhosa to homologous rabbit antiserum, and (3) the exposure of pneumococci to homologous rabbit antiserum. In the first instance changes occurred due to penetration of the metal ions into the bacterial cell and interaction with the inner bacterial protoplasm. In the second instance a surface film formed, whose thickness was compatible with its monomolecular antibody structure. In the third instance the capsule increased in thickness many times the diameter of the globulin molecule. This change was compatible with the interpretation that the polysaccharide molecules of the capsule of the pneumococcus form a gel into whose interstices the antiserum molecules penetrate.

The author points out that the electron microscope, by revealing the structural changes caused by antibacterial agents, is of value for an understanding of the mechanism of such agents.

PLATT, Gouverneur, N. Y.

MOSQUITO VECTORS AND INAPPARENT ANIMAL RESERVOIRS OF ST. LOUIS AND WESTERN EQUINE ENCEPHALITIS VIRUSES. W. MCD. HAMMON, W. C. REEVES and M. GRAY, Am. J. Pub. Health **33**:201 (March) 1943.

During a series of correlated field and laboratory studies in the Yakima Valley, Washington, both the St. Louis and the western equine virus were isolated repeatedly from one species of mosquito. Antibodies for both viruses were found in as high as 50 per cent of apparently healthy domestic fowl in that area. These findings, together with other reports in the literature, led the authors to formulate a hypothesis of a mosquito-animal-mosquito cycle for both viruses. Field laboratory experiments in Yakima showed that mosquitoes could transmit the St. Louis virus from one fowl to another. These experiments indicated that at least three genera of mosquitoes are potential vectors. Studies with the western equine virus gave similar results The authors concluded that both types of encephalitis are mosquito borne and that there probably exists an inapparent animal reservoir. Control should be directed primarily at the arthropod vectors, with human vaccination employed under special circumstances.

PLATT, Gouverneur, N. Y.

FLAVICIN: AN ANTIBACTERIAL SUBSTANCE PRODUCED BY AN ASPERGILLUS FLAVUS. MILTON T. BUSH and ANDRES GOTH, J. Pharmacol. & Exper. Therap. **78**:164 (June) 1943.

This substance was highly bactericidal to certain staphylococci and streptococci, to Corynebacterium diphtheriae and to Bacillus anthracis but relatively nontoxic to several other organisms. It was nontoxic to mice in doses many times the therapeutic dose.

PILCHER, Cleveland.

EFFECT OF PROPYLENE GLYCOL ON BACTERIAL SPORES. EDWARD BIGG, Proc. Soc. Exper. Biol. & Med. **53**:120 (June) 1943.

Suspensions of spores of Bacillus subtilis were atomized into a chamber containing propylene glycol vapor, but no antibacterial action was obtained such as occurred when suspensions of the vegetative forms were treated in the same manner. No effect on the viability of these spores occurred when propylene glycol was added to cultures, even though the spores were exposed as long as seventy-two hours. The fact that propylene glycol in either its liquid or its vapor state has no killing effect on the spores tends to support the hypothesis that the bacterial action of the glycols is due to the hygroscopic properties of these substances.

HANSEN, Minneapolis.

Metabolism; Infant Feeding; Milk and Other Foods

SURVEYS OF THE NUTRITION OF POPULATIONS—PART 2. JOHN B. YOUMANS, E. WHITE PATTON and RUTH KERN, Am. J. Pub. Health **33**:58 (Jan.) 1943.

This is part II of a report of a nutritional survey of a rural community of 1,200 inhabitants in middle Tennessee. Individual nutritional status was studied by means of records of food intake, history, physical examination and laboratory tests. The nutritional status, as it relates to calory intake, was determined principally by the measurements of food consumption and of body weight. Compared with the recommended allowance of the Food and Nutrition Board of the National Research Council, the calory intake of all groups, except white children between 1 and 6 years of age, was moderately to severely deficient. However, malnutrition as evidenced by underweight was not always correlated

with inadequate calory intake. This may be due, in part, to the establishment by the National Research Council of unnecessarily high calory standards.

PLATT, Gouverneur, New York.

NUTRITIONAL NEEDS OF AMERICAN YOUTH. H. D. KRUSE, Am. J. Pub. Health **33**:249 (March) 1943.

Severe acute deficiency disease is rare in the United States, but mild acute, mild chronic and severe chronic forms have recently been recognized as widespread. Usually the acute form is superimposed on a chronic condition. Most of the changes associated with chronic deficiency states have been mistakenly attributed to senescence. Actually they are the result of deficiencies developing slowly over a lifetime. These chronic processes may begin in childhood. The lower the economic level, the more frequently, the more severely and the earlier in life they occur.

It has been taught that conversion to an optimum diet is all that a person needs for correction of his dietary deficiency. However, specific therapy is needed for complete and effective treatment of deficiency states. It has also been thought that deficiency diseases respond dramatically to therapy. This is true of the acute forms, but the lesions associated with the chronic forms are more stable and may persist for as long as several years. In view of this, chronic deficiency states, which start in youth, should be corrected before they have advanced to the late stages, which will require a long period of therapy. There are strong indications that these deficiency conditions predispose to more serious diseases. If this is true, the earlier they are corrected, the less morbidity and premature mortality there should be.

Although correction is necessary, prevention is ideal. Prevention depends on proper diet, and education in proper dietary habits should begin early in life. Much more work along these lines should be done in the schools. The school program should include diagnosis and correction of deficiency states in the students, education in diet and provisions for a school lunch room conducted according to dietetic principles.

Nutrition is a matter not only of economics but of agriculture, food technology, education, medicine, public health, chemistry and physics. No other science cuts across so many specialties. Unless the activities of all these groups are consolidated, progress will not be as rapid as it should be.

PLATT, Gouverneur, New York.

COMPARATIVE NUTRITIVE VALUE OF BUTTER FAT AND VEGETABLE OILS. E. B. HART, Am. J. Pub. Health **33**:265 (March) 1943.

Experiments at the University of Wisconsin indicate the superiority of butter fat over certain vegetable oils (such as corn oil, cottonseed oil, soy bean oil and coconut oil) for the growth of young rats. The factor involved is not a vitamin or a phosphatide. It appears to be a saturated fatty acid (or acids) of high molecular weight present in the saponifiable portion of the butter fat. The author concludes that reenforcement of a vegetable oil with vitamins A, D and E will not make it equal in nutritive value to butter fat.

PLATT, Gouverneur, New York.

THE VALUE OF DAIRY PRODUCTS IN NUTRITION. ROYAL A. SULLIVAN, EVELYN BLOOM and JOAN JARMOL, J. Nutrition **25**:463 (May) 1943.

Twelve different types of cheese were analyzed for riboflavin, pantothenic acid, nicotinic acid and biotin. Only minor variations in the concentrations of riboflavin were noted. However, the amounts of the other factors present were dependent on the age of the cheese and the ripening process used.

FREDEEN, Kansas City, Mo.

THE EFFECT OF DIETARY FAT ON BONE CALCIFICATION IN THE GROWING RAT. RUDOLF BUNKFELDT and HARRY STEENBOCK, J. Nutrition **25**:479 (May) 1943.

When cottonseed oil was included in a low phosphorus, cereal-free rachitogenic ration for rats, calcification was decreased uniformly and in proportion to the amount of fat fed. The source of the phosphorus (phytic acid or inorganic phosphates), the high or low calcium-phosphorus ratio (6:1, 3:1, 1:1) and the presence or absence of vitamin D did not alter the results. The investigators substituted fibrin, yeast and starch for egg white, rice bran and dextrose, respectively, and the result was the same. When cottonseed oil was given in a diet which was optimal in phosphorus content, calcification increased to a pronounced degree, with more than optimal phosphorus content the increase was less evident. With rations containing 0.25 per cent of phosphorus, a fourfold increase in the calcium-phosphorus ratio still permitted the beneficial effect of fat; however, a sixfold increase almost eliminated it.

FREDEEN, Kansas City, Mo.

Vitamins; Avitaminoses

LOCALIZED VERTICAL GROWTH DISTURBANCE. D. D. GLUCKSMAN, J. Am. Dent. A. **29**:184 (Feb.) 1942.

The author reports a case in which all deciduous molars were left behind because of lack of vertical growth in these areas. Such lack of vertical growth may be present in either deciduous or permanent dentition, and the affected teeth may become submerged and eventually simulate impacted teeth.

BLACK, Berkeley. [ANGLE ORTHODONTIST]

DANGEROUS EFFECTS OF VITAMIN D OVERDOSAGE ON DENTAL AND PARADENTAL STRUCTURES. HERMANN BECKS, J. Am. Dent. A. **29**:1947 (Nov.) 1942.

Previous reports on this subject show a great deal of variation; results are not comparable in many instances owing to the fact that different sources and quantities of vitamins were used in different experiments, basal diets and duration of experiments differed and animals differed in species and ages. In this study two litters of thoroughbred cocker spaniels were used; specimens were studied roentgenographically and histologically. It was found that with overdosage of vitamin D the growth and development of jaws and teeth are retarded; optimum amounts of vitamins A and D favor production of strong teeth and jaws, while optimum amounts of vitamin D and excessive amounts of vitamin A are even more favorable for growth of jaws and teeth. Generalized osteosclerosis of the jaw bone and the paradental structures, malformed teeth, pulp stones and malocclusion follow the administration of excessive amounts of vitamin D, although the effects are less pronounced when tuna oil rather than irradiated ergosterol is the source of the vitamin D. Excessive vitamin A decreases the injurious effects of excessive vitamin D. The indiscriminate use of vitamin D therapy is potentially harmful; natural fish oils are less dangerous than the irradiated products.

WYLIE, San Francisco. [ANGLE ORTHODONTIST]

THE BIOLOGICAL DETERMINATION OF VITAMIN E. HOWARD GOTTLIEB, FORREST W. QUACKENBUSH and HARRY STEENBOCK, J. Nutrition **25**:433 (May) 1943.

Gottlieb, Quackenbush and Steenbock used a new diet with low fat content for vitamin E assays and presented a new criterion (the increase in weight during gestation) for the biologic determination of the content of vitamin E. For an equal response, the requirement for vitamin E with the diet low in fat was less than half of that with a diet high in fat. Synthetic alpha, beta and gamma tocopherols and alpha tocopherol acetate had relative biologic activities of 100, 25, 19 and 100, respectively. FREDEEN, Kansas City, Mo.

THE EFFECT OF AROMATIC HYDROCARBONS ON GROWTH: THE REVERSIBLE INHIBITION OF PANTOTHENIC ACID BY SULFAPYRIDINE. HAROLD D. WEST, NELSON C. JEFFERSON and RAVEN E. RIVERA, J. Nutrition **25**: 471 (May) 1943.

A synthetic diet low in casein which contained sulfapyridine alone or together with l-cystine or dl-methionine induced symptoms of pantothenic acid deficiency in rats; supplemental administration of calcium pantothenate reversed the condition. Since pantothenic acid is necessary for the growth of the rat, it was assumed that two growth-inhibiting mechanisms were at work, a direct effect, due to sulfapyridine and relieved by either l-cystine or dl-methionine, and an indirect effect, due to inhibition of pantothenic acid by sulfapyridine. FREDEEN, Kansas City, Mo.

THE INFLUENCE OF VARIETY, SIZE AND DEGREE OF RIPENESS UPON THE ASCORBIC ACID CONTENT OF PEACHES. G. M. SCHRODER, G. H. SATTERFIELD and ARTHUR D. HOLMES, J. Nutrition **25**:503 (May) 1943.

The authors found that the content of ascorbic acid in peaches was lower than that in lemons, oranges or tomatoes but that fully ripe peaches contain sufficient ascorbic acid to contribute to the human requirements. The average amount of ascorbic acid in ripe peaches varied from 3.84 to 12.86 mg. per hundred grams for the Augbert and Hiley Belle varieties respectively. There was no correlation between the size of the peach and the amount of ascorbic acid it contained; however, the content of ascorbic acid increased with the ripeness. FREDEEN, Kansas City, Mo.

THE RELATION OF SEASON, WEIGHT AND PRICE TO THE VITAMIN C CONTENT OF ORANGES. ARTHUR D. HOLMES, JAMES A. PATCH and FRANCIS TRIPP, New England J. Med. **228**:8 (Jan. 7) 1943.

Oranges were purchased in local retail stores and from hucksters under average conditions. The juice was removed and assayed for its vitamin C content. The amount of vitamin C per 100 cc. of orange juice in the March samples averaged 52 Mg.; in June, 45 mg.; in September, 39 mg.; in December, 56 mg. The cost of 75 mg. of vitamin C was 4.8 cents in March, 5.9 cents in June and September and 3.6 cents in December. GENGENBACH, Denver.

THE TOCOPHEROL LEVEL IN HUMAN SERUM DURING ORAL TOCOPHEROL THERAPY. ISRAEL S. WECHSLER, GERDA GERNSHEIM MAYER and HARRY SOBOTKA, Proc. Soc. Exper. Biol. & Med. **53**:170 (June) 1943.

The level of tocopherol in the serum of 17 untreated persons with amyotrophic lateral sclerosis was 0.67 mg. per hundred cubic centimeters, and in the serum of 14 patients with miscellaneous myopathies it was 0.61 mg. per hundred cubic centimeters. The administration of 75 mg. of alpha tocopherol a day did not affect the serum level; the administration of 100 mg. a day caused a rise of 0.27 mg. in the serum level in the patients with amytrophic lateral sclerosis. Doses above 200 mg. a day increased the levels in these patients as much as doses of 340 to 740 mg. Patients with amyotrophic lateral sclerosis showed greater clinical improvement when they were receiving the higher doses and consequently had higher levels of tocopherol in the serum. Tocopherol could not be detected in the spinal fluid. HANSEN, Minneapolis.

ON TESTING DARK ADAPTATION. W. J. B. RIDDELL, Glasgow M. J. **21**:149 (June) 1943.

The author discusses the testing of dark adaptation but states that the methods used at present are not accurate unless carried out for a considerable period at each test. This prolonged testing period makes them of little value for clinical application, but they will prove a fruitful approach in physiologic research until all the factors which are concerned in dark adaptation are known. SNELLING, Toronto, Canada.

ESTIMATION OF "TRUE" ASCORBIC ACID IN URINE. DEREK RICHTER and PHYLLIS GODBY CROFT, Lancet **1**:802 (June 26) 1943.

For urines containing a normal or low amount of ascorbic acid titration with dichlorophenolindophenol does not give the true content of ascorbic acid owing to the presence of sodium thiosulfate, which also decolorizes the indophenol dye. In the method described here the thiosulfate is precipitated with lead acetate and removed before titration. LANGMANN, New York.

Hygiene; Growth and Nutrition; Public Health

AFFECTIVITY AND GROWTH IN CHILDREN. ELIZABETH MECHEM, Child Development **14**:91 (June) 1943.

The writer has attempted to adapt the role played by affectivity (general feeling state) to the concept of the child as a whole. Sixty-five University Elementary School children ranging in age from 7 to 12½ years served as subjects for the study. Of this number, 44 remained to be interviewed a second time during the following year. Affectivity scores derived from interviews administered during each year of the study were correlated with various other measures of growth in the children studied. In addition, for the children who had two consecutive interviews, analysis was made of the change in affectivity scores which took place in the interval. In general, the results suggest that for the population studied, overt behavior and pulling of covert feeling into words bear demonstrated relationships to each other. These relationships are multiple in that many factors of (such as mental age, achievement, maturity of interest and rate of growth seem to limit and modify each measure of relationship. [CHILD DEVELOPMENT ABSTRACTS.]

MENARCHEAL AGE AND THE HEIGHT, WEIGHT AND SKELETAL AGE OF GIRLS AGE SEVEN TO SEVENTEEN. KATHERINE SIMMONS and WILLIAM W. GREULICH, J. Pediat. **22**:518 (May) 1943.

A comprehensive study of maturation factors (chronologic age at menarche, skeletal maturation, standing height and weight) and their interrelationship was

made on 200 girls of Brush Foundation. These girls were examined each birthday from the age of 7 to 17 years.

In general, from 7 to 15 years of age, girls with early menarche were taller than those with late onset of the menstrual function. Also from 7 to 16 years of age girls with early menarche had a greater mean weight and a greater weight-height ratio. They were also advanced in mean skeletal age. The greatest increment in height, on the average, occurred during the year preceding the menarche. Girls with early menarche experienced the greatest acceleration in height followed by the greatest deceleration, whereas girls with late menarche had slight increase and less deceleration. Maximal rate of increase in height never occurred after the menarche. Skeletal age was more accurate than weight and height as a basis for determination of menarcheal age and could be assessed in advance of the premenarcheal acceleration of weight and height.

STETTENBENZ, Buffalo.

DEVELOPMENTS IN SOCIAL ASSISTANCE TO CHILDREN IN URUGUAY. ROBERTO BERRO, Bol. Inst. internac. am. de protec. a la infancia **15:** 587 (April) 1942.

The author in his lecture about the manner in which social assistance to children in Uruguay is carried out gives an explanation of the work and refers to the ten attainments that in his judgment have been incorporated in the Children's Code, ratified in 1934, granting to the Uruguayan child the following rights: (1) to be born healthy; (2) to be breast fed; (3) to know his parents; (4) not to be neglected; (5) to live in a well constituted home; (6) to grow under medical supervision; (7) to be instructed; (8) to be educated; (9) to be judged as a child, and (10) to be protected at work.

FROM EDITOR'S SUMMARY.

THE LAW IN BEHALF OF SOCIAL DEFENSE FOR CHILDREN. MONTEVIDEO, URUGUAY. SOFÍA ALVAREZ VIGNOLI DE DEMICHELI, Bol. Inst. internac. am. de protec. a la infancia **15:**608 (April) 1942.

The author refers to the position of the child within the law and states that it was at the end of the nineteenth century that the child began to be a source of preoccupation as a subject of law and that besides consecrating the rights peculiar to the child, inherent to his personality and different from those of the adult the problems of childhood were wholly and in their mutual relations considered from medical, pedagogic, juridical and social points of view.

Specially referring to Uruguay, the author recalls the laws in relation to child protection, such as those about compulsory education (1877 and 1885), vagrancy (1882), protection to minors (1911), bureaus for delinquents and minors (1915), intermediaries in shady transactions (1916), night work (1918), protection to nursing infants (1919), compulsory weekly rest (1920), and loss of paternal authority (1928), and to the Children's Code (1934).

The treatment of children who have committed a social fault should be based on three fundamental principles: (*a*) individualization of the subject; (*b*) supervised liberty, and (*c*) indetermination of the sentence. To attain these the doctor, the teacher and the social worker must collaborate, giving the Judge of Minors the necessary information in order that he, as a "good father," having in mind the interests of the child and those of society, may determine what he considers necessary.

The author discusses in detail some problems, such as the supervised liberty of the minor in his own home, the elimination of preventive prison and the establishment of detention homes; she also refers to illegitimacy, to adoption as it was before and as it is now, to investigation of paternity and to pensions for food.

FROM EDITOR'S SUMMARY.

PROGRESS IN THE DEVELOPMENT OF ECONOMIC AND SOCIAL SERVICES FOR FAMILIES AND CHILDREN. BRYAN J. MCENTEGART, Bol. Inst. internac. am. de protec. a la infancia **16:**351 (Jan.) 1943.

This brief review covers progress in both North and South American countries. The principal tendencies noted are the consideration of special provisions for the working mother before and after confinement, the extension of social insurance laws, the establishment of national bureaus for the care of children, the increase of special courts for children throughout the countries of Central and South America, the abandonment of large institutions for the care of dependent children with emphasis on the use of foster homes or small units, and the increase in education for social service.

LESLIE, Evanston, Ill.

Prematurity and Congenital Deformities

MEDICAL SOCIAL PROTECTION OF THE PREMATURE CHILD. JULIO A. BAUZÁ, Bol. Inst. internac. am. de protec. a la infancia **15:**633 (April) 1942.

In every advanced country the protection of premature babies or of those weak at birth is imperative, not only in the cities but in the country, and special attention should be given to it by the associations for child protection.

A central service is necessary with all the modern technics for the boarding of the premature infants who cannot be adequately assisted in the family environment.

This central service should be provided with the adequate material necessary for the transportation of the premature babies without any risks; also it should have a technical and an auxiliary staff for the supervision of the infants.

When the medical examination takes place at the infant health clinic the transportation of the babies should be delayed as long as possible, especially in the cold season, to avoid the long waiting at the clinic.

The supervision of those children at their homes should be in charge of specialized social workers; when the mother or the social worker asks for medical assistance, the doctors of the infant health center should assist the child. In order to obtain a better result the cooperation of the motherhood services with those services relying on the Children's Council should be required; also it would be a good thing to insist on the strict fulfilment of the requirement to make known all the children who are born weighing less than 2,500 Gm. or with signs of limited vitality.

The prenatal care of the mother, including rest and adequate nourishment during the last months of pregnancy, will considerably reduce the number of children born with low vitality.

In order to exercise a favorable influence on infant mortality during the first month or neonatal mortality, specially due to premature or congenital weakness, it should be necessary to apply to the motherhood services, as well as to the services relying on the Children's Council, the necessary and the efficacious modern means which other countries have already proved to be efficient.

EDITOR'S SUMMARY.

Acute Contagious Diseases

HYPOTHETICAL RELATIONSHIP OF WATER SUPPLIES TO POLIOMYELITIS. KENNETH F. MAXCY, Am. J. Pub. Health **33**:41 (Jan.) 1943.

The author discusses the hypothesis that poliomyelitis is a water-borne disease. Of fundamental importance in this problem is the question of how the virus enters and leaves the body. Animal experiments and post-mortem studies of human tissue indicate that the virus enters through the alimentary tract. It has not been determined whether it is conveyed by air particles or by contaminated food or drink. From laboratory studies it is not clear whether nasopharyngeal secretions or intestinal discharges or both are of importance as portals of exit for the virus en route to new hosts. Recent studies have focused attention on intestinal discharges by showing that the virus may be present in stools of persons not clinically ill as well as in stools of persons with recognizable poliomyelitis. The virus has also been isolated from domestic sewage. It is theoretically possible that virus in polluted water can survive the process of treatment used in purifying water prior to human consumption. Whether the concentrations of chlorine ordinarily used in treatment of water for drinking or for swimming pools are sufficient to inactivate the virus is still uncertain. With one possible exception, poliomyelitis virus has never been demonstrated in water used for drinking or bathing. This in itself does not exclude the possibility that poliomyelitis may be water borne.

However, before poliomyelitis, or any other disease, can be considered water borne it must be convincingly shown that its behavior in human communities is such as would be expected if the causative micro-organism were dependent for continued dissemination, in part or at times, on the medium of contaminated water. Unlike diseases known to be water borne, like dysentery and typhoid, the incidence of poliomyelitis cannot be correlated with the degree of sanitation of the environment or with the quality of the water used. Furthermore, in spite of a large number of investigations by competent observers, there is no record of an explosive outbreak of poliomyelitis which has been attributed to simultaneous exposure of a group of people to a common water supply.

The author concludes that at present there is insufficient evidence to justify the belief that water is a medium of any practical importance in the spread of poliomyelitis. PLATT, Gouverneur, N. Y.

EPIDEMIOLOGICAL AND EXPERIMENTAL OBSERVATIONS ON THE POSSIBLE SIGNIFICANCE OF RODENTS IN A SUBURBAN EPIDEMIC OF POLIOMYELITIS. CLAUS W. JUNGEBLUT and GILBERT DALLDORF, Am. J. Pub. Health **33**:169 (Feb.) 1943.

A localized outbreak of 5 cases of poliomyelitis, in which 2 patients with bulbar paralysis died and 3 extensively paralyzed patients recovered, occurred in White Plains, Westchester County, N. Y., in the fall of 1942. From the brain of a dead gray house mouse, found in the basement of the home of one of the patients who died, an infectious agent was isolated, which was transmissible in albino mice by the intracerebral and the intraperitoneal routes. There were marked nervous symptoms, resulting in death of most of the infected animals and frequently in complete flaccid paralysis of one or more extremities. The lesions in the spinal cords of the infected mice resembled those found in mice suffering from Theiler's disease or in mice paralyzed by infection with either the mouse-adapted Lansing or the S K murine strain of human poliomyelitis virus. The infectious agent passed easily through a Seitz filter. It was neutralized to a considerable extent by serum from 2 of the 3 convalescent patients as well as by serum from a normal adult mouse.

From the brain and the spinal cord of 1 of the dead patients a virus was isolated in a hamster, which was thereafter transmissible in albino mice by the intracerebral and the intraperitoneal route. It caused typical and severe poliomyelitic lesions in the entire central nervous system. This virus was about 10 millimicrons in diameter.

Both the virus isolated from the dead mouse and that from the dead patient were inactivated completely by antiserum against Theiler's virus of mouse encephalomyelitis and partly by convalescent serums from patients in this outbreak. The human virus is much more potent than the mouse virus.

PLATT, Gouverneur, N. Y.

ATTITUDE OF THE NATION TOWARD IMMUNIZATION PROCEDURES. LEONA BAUMGARTNER, Am. J. Pub. Health **33**:256 (March) 1943.

A nation-wide poll among white persons was conducted in September 1941 regarding immunization against typhoid, smallpox and diphtheria. An adequate sample of about 3,000 persons was questioned. It was found that between 80 and 90 per cent believed that active immunization would prevent these diseases or modify their severity. Most persons thought that these diseases were sufficiently serious to cause concern. Few knew of any serious drawback to immunization procedures. Of those not previously immunized, 50 per cent stated they might be willing to be immunized. Eighty per cent of the mothers of children not immunized answered affirmatively. However, most of the persons questioned did not know when immunization procedures were indicated. Most of them, including a large number of mothers, thought that immunization was necessary only after exposure. Even those mothers who thought routine protection necessary believed 6 years of age the proper time to protect children against smallpox and diphtheria. Only 3 per cent of the mothers stated that they would have their children protected before 1 year of age. There was similar lack of information regarding the number of injections necessary to protect against diphtheria and the duration of immunity following immunization against diphtheria and smallpox.

The author concludes that a great deal of education is still necessary but that, in general, public opinion is sufficiently favorable toward active immunization against smallpox, diphtheria and typhoid that public health officials and private physicians can well urge it as a routine practice. PLATT, Gouverneur, N. Y.

VARICELLA FOLLOWING EXPOSURE TO HERPES ZOSTER. JOSEPH GARLAND, New England J. Med. **228**:336 (March 18) 1943.

The mother of 2 children, a daughter aged 8 years and a son aged 6, first noticed soreness of the left side of her throat on January 23. By January 28 pain and swelling of the left side of her face had developed, and on January 30 a typical eruption of herpes zoster appeared on this area. She had had varicella

in childhood. Fourteen days after her first symptoms had appeared, the son showed the scattered papules of an eruption that became well defined varicella twenty-four hours later, and on the following day the husband and the daughter broke out with typical, moderately severe chickenpox. No exposure to chickenpox had occurred for any of the 3. The daughter had been confined to the house with a cold since the beginning of her mother's illness, and no attacks of the disease had occurred in the small school group of which the son was a member.

GENGENBACH, Denver.

OBSERVATIONS ON THE KENNY TREATMENT OF POLIOMYELITIS. F. H. KRUSEN, Proc. Staff Meet., Mayo Clin. **17**:449 (Aug. 12) 1942.

The Kenny concept of poliomyelitis is apparently in no conflict with the accepted proof of damage to the anterior horn cells and flaccid paralysis. It asserts, however, that early in the disease the major symptoms are not so much flaccid paralysis as "muscular spasm," "incoordination" and "mental alienation."

Krusen found that muscular spasm occurs during the early stages of poliomyelitis, that it may be widespread and that it is something more than the result of meningeal irritation, as was previously thought. The principal sites of such spasms are the hamstring muscles; the muscles of the back and neck; the gastrocnemius, pectoral, quadriceps and biceps muscles, and the muscles of respiration. The Minneapolis investigators of the Kenny concept define muscular spasm as a group of symptoms, including fibrillary twitchings (fasciculation), hyperirritability of the muscle to stretching and a more or less tonic state of contraction of the muscle fibers, which frequently cannot be overcome even by great force.

Incoordination is defined as "(1) that due to the spreading of motor impulses intended for a certain muscle to other muscles or groups of muscles due to such condition as pain on attempted motion of the involved muscle or inability of that muscle to perform its proper function; (2) that occurring within the involved muscle itself, so that ineffective contraction is produced instead of a coordinated rhythmic contraction producing maximum motion at the insertion of the muscle."

Mental alienation is defined as "inability to produce a voluntary, purposeful movement in a muscle in spite of the fact that the nerve paths to that muscle are intact. This is a physiologic block which must be distinguished from the organic interruption resulting from the destruction of anterior horn cells by the disease." The Minneapolis workers suggest that the most frequent mechanisms for the production of mental alienation may be stated as follows: 1. A muscle is pulled beyond its normal resting length by its opponent, which is in spasm. 2. A muscle may become "alienated" when pain is produced in its involved opponent by the attempt of such unaffected muscle to contract. 3. The spasm, or its subsequent results, in an affected muscle may be so severe that the braking action, or check, on the normal, opposing muscle may discourage the latter enough to produce its "alienation." 4. The disease may produce changes in the nervous system which do not actually destroy the cells or fibers but cause loss of conduction power and interfere with normal neuromuscular action. Thus, in the case of foot drop the gastrocnemius muscle is the one affected and is to be regarded as in spasm, the dorsiflexors of the foot suffering from "mental alienation."

Krusen asserts that "the tremendous enthusiasm for the Kenny procedure seems to a large degree warranted, although it appears evident that some of the claims concerning it are too enthusiastic." The claim that no deformities follow the procedure seems untrue, since deformities appear to develop in some cases. Krusen agrees that contractures, malalinements and spinal curvatures do not follow the treatment.

ALPERS, Philadelphia.
[ARCH. NEUROL. & PSYCHIAT.]

THE KENNY VERSUS THE ORTHODOX TREATMENT OF ANTERIOR POLIOMYELITIS. J. ALBERT KEY, Surgery **14**:20 (July) 1943.

The outstanding difference between the Kenny and the orthodox treatment of poliomyelitis may be stated as follows: In the acute febrile stage Sister Kenny advises active treatment with hot fomentations for relief of muscle spasm, and with the orthodox technic absolute rest and quiet are ordered. The Kenny method avoids the use of casts or splints and begins active muscle reeducation before pain and tenderness have subsided. The author presents evidence to show that the experience has aggravated and prolonged pain and tenderness. The advocates of the Kenny method believe that braces or splints interfere seriously with circulation and cause hopeless muscular atrophy and stiffness. The author states that this does not occur if these aids are properly applied and counters with the statement that the Kenny method causes more extensive atrophy and stiffness than the orthodox treatment in that the patient is kept flat on the back for six months or longer and is turned for treatment only for one hour daily. This is more complete and longer immobilization than is advocated under the orthodox regimen. The tendency of muscles to contract (muscle spasm) subsides when the pain and tenderness disappear, and if deformities are prevented the symptoms of spasm contractures rarely constitute an important problem under orthodox treatment. The hot packs may cause furuncles and burns, and manipulations of the Kenny method do not prevent the stretching of paralyzed muscles.

An evaluation of the results of the orthodox treatment in a series of cases of poliomyelitis, in accordance with the criteria by which the Kenny method is judged, reveals that the rate of recovery with the use of orthodox methods was as high as that with the Kenny technic, or higher. The author points out that cure is obtained under orthodox methods with far less cost, less risk to life, less time and less labor.

SHENKIN, Philadelphia.
[ARCH. NEUROL. & PSYCHIAT.]

LEDERLE'S PERTUSSIS ANTIGEN IN TREATMENT OF WHOOPING-COUGH: REPORT OF AN INVESTIGATION. RICHARD S. W. BAKER, Brit. M. J. **1**:562 (May 8) 1943.

In 1940 Joslin and Christensen claimed that if Lederle's detoxified pertussis antigen was given in sufficient doses and at suitable intervals it would shorten the duration of the disease and minimize the incidence of complications. Baker observed 20 patients with pertussis treated with 2 cc. of antigen intramuscularly at two day intervals and 20 controls who appear to have been fairly selected. His results showed no appreciable difference in the average duration of hospitalization, the severity of the disease or the incidence of complications, between the controls and those treated with antigen. Blood smears taken at weekly intervals, as an evidence of

cessation of the disease, also showed no appreciable difference between the two groups.

Baker concluded that the use of Lederle's pertussis antigen was of no value in treating whooping-cough that has progressed as far as the paroxysmal stage.

BIRDSONG, Charlottesville, Va.

EXPERIMENTAL MUMPS: TRANSMISSION OF THE DISEASE TO MONKEYS; ATTEMPTS TO PROPAGATE THE VIRUS IN DEVELOPING HEN'S EGGS. C. SWAN and J. MAWSON, M. J. Australia **1**:411 (May 8) 1943.

Of 14 attempts to transmit mumps to monkeys by intraparotid inoculation of human saliva collected from 36 patients with mumps, 3 were successful. The positive results were obtained from inoculations of saliva collected from 4 patients within four to twelve hours of the onset of parotitis. In 6 attempts to isolate the virus by the use of the cerebrospinal fluid of patients suffering from meningoencephalitis following mumps, positive results were obtained with fluid from only 1 of 4 patients. By injecting suspensions of the excised parotid glands of the animals thus affected, it was possible to transmit the disease in series (three passages). Two of 8 attempts to cultivate the virus of mumps in developing hen's eggs gave suggestive, but not positive, results. Rabbits, mice, a guinea pig and dogs remained well when inoculated with the virus by various routes.

GONCE, Madison, Wis.

Acute Infectious Diseases

TETANUS TOXOID: ITS USE IN THE UNITED STATES ARMY. ARTHUR P. LONG, Am. J. Pub. Health **33**:53 (Jan.) 1943.

In 1941 the United States Army started routine immunization of its personnel against tetanus. All military personnel are given a series of three injections of 1 cc. of fluid tetanus toxoid subcutaneously at intervals of three weeks. After one year a single stimulating dose of 1 cc. is administered. A similar dose is given prior to departure for a theater of operations except when less than six months has elapsed since the last injection. Whenever tetanus becomes a possibility (after wounds, burns, etc.) a stimulating dose of toxoid is administered. Antitoxin is administered for prophylaxis only when the person has not received at least the initial series of injections of toxoid.

Two types of reactions have been noted. One type consists of headache, weakness, general malaise, local soreness and occasionally chills and fever. The second type usually starts within thirty minutes after the injection. The most common manifestations are flushing and itching of the skin, local and generalized urticaria and edema of the lips and the eyelids. Occasionally edema of the glottis and dyspnea are noted. Early in the immunization program 0.05 per cent of the injections were followed by the second type of reaction. Intradermal tests revealed sensitivity to some constituent of the toxoid. About 85 per cent of the reactions of sensitivity occurred after the second or third dose, which indicates that at least some of the reactors had been sensitized by previous injections. Investigation showed that toxoids containing Witte or Berna peptones (carried over from the original culture mediums) were responsible for at least six times as many reactions of sensitivity as were toxoids free of these two peptones. Discontinuance of toxoids containing Witte and Berna peptones decreased greatly the incidence of reactions. Experiments in producing toxin on protein-free or similar non-reaction-producing mediums are now under way. Use of toxoid produced from such toxin may eliminate all such reactions.

Large scale studies for the determination of antitoxin levels of the blood after immunization have not been made. Since June 1941 only 4 cases of tetanus have been reported from the Army. None of the affected persons had been immunized.

PLATT, Gouverneur, N. Y.

MILK-BORNE OUTBREAKS DUE TO SEROLOGICALLY HEMOLYTIC STREPTOCOCCI. T. D. DUBLIN, E. F. H. ROGERS, J. E. PERKINS and F. W. GRAVES, Am. J. Pub. Health **33**:157 (Feb.) 1943.

In the period 1917 to 1941 the New York State Department of Health investigated 168 outbreaks of milk-borne disease, which affected 9,989 persons. All except 4 outbreaks were due to raw milk. There was a total of 57 outbreaks of scarlet fever and septic sore throat, which affected 6,812 persons.

In recent years the Lancefield classification of hemolytic streptococci has been utilized extensively in the search for the source of milk-borne outbreaks of scarlet fever and septic sore throat. Of the strains pathogenic for man, 95 per cent are of group A. The pathogenic strains have been further differentiated by Griffith into thirty or more serologically specific types. This classification provides a more exact means of identification of the source of milk-borne outbreaks and also permits further study of the epidemiologic characteristics of the different strains of this organism. Since 1936 there have been at least six reports of the use of Griffith's classification in such studies, all in foreign literature. In 3 of these outbreaks, the Griffith type of strain was incriminated. Hemolytic streptococci isolated in 9 outbreaks since 1935 in the state of New York, exclusive of New York city, were typed. Type 3 was identified in 3 outbreaks. No other type was encountered more than once.

A detailed account is given of an epidemiologic investigation of an outbreak of 8 cases of scarlet fever and 36 cases of septic sore throat in a small community, of approximately 275 inhabitants, which occurred in April 1942. Cultures from the throat were obtained from 35 of the 44 patients during or shortly after their acute illness. Of the 23 cultures which yielded hemolytic streptococci, 17 were identified serologically as group A. Of these, 15 were of Griffith's type 3. The outbreak was traced to a cheese factory receiving daily 2,029 cans (40 quart size) of milk supplied by 356 producers from 6,069 cows. A Breed smear was made from samples of each can. The presence of chained streptococci or of excessive numbers of leukocytes led to further study of 73 of the 356 herds. The 73 farms were visited, each cow examined and information with respect to history of injury to a teat or human illness obtained. From 55 of these herds, 150 quarter samples of milk were collected. In 17 of these, hemolytic streptococci were found, but in only 1 were they of Lancefield's group A. This strain was further identified as Griffith's type 3. One of this cow's teats had been injured six weeks before the outbreak. Three persons on the farm gave histories of recent illness, 1 of scarlet fever and 1 of severe sore throat. From 2 of these 3 persons streptococci of Griffith's type 3 were isolated, thus demonstrating the source of the outbreak.

By means of throat cultures obtained at the time of the outbreak and one and two months later, the prevalence of streptococci of type 3 in the community was determined. At the time of the last survey no streptococci of type 3 were found.

PLATT, Gouverneur, N. Y.

AN OUTBREAK OF TYPHOID FEVER DUE TO THE SMALL COLONY VARIETY OF EBERTHELLA TYPHOSA. JANIE F. MORRIS, CATHERINE G. BARNES and T. F. SELLERS, Am. J. Pub. Health **33**:246 (March) 1943.

Thirteen cases of typhoid occurred in a family group of Negroes in Georgia. From stools of 11 of them (2 died before stools could be obtained) a small colony variety of Eberthella typhosa was isolated. Only one epidemic due to this variety has been reported previously. On beef extract and beef infusion agar the colonies averaged 0.2 to 0.3 mm. in diameter after twenty-four to forty-eight hours' incubation. On Endo's agar and bismuth sulfite plating mediums, which contain utilizable sulfur, the colonies grew to a diameter of 1 to 2 mm. On Russell's or Krumwiede's sugar slants and butts the growth was scanty and the reaction acid. The authors point out the advisability of using a plating medium containing utilizable sulfur for the cultivation of enteric organisms to avoid the possibility of missing the small colony variety of E. typhosa.

PLATT, Gouverneur, N. Y.

SPORADIC INFECTIONS CAUSED BY SALMONELLA SUIPESTIFER AND SALMONELLA ORANIENBURG. B. V. JAGER and MARION E. LAMB, New England J. Med. **228**:299 (March 11) 1943.

Six sporadic cases of infection with Salmonella suipestifer in human beings are described. Clinically these cases showed great variation. The bacteriologic identification of this organism and its separation into types are discussed. Two cases of infection with Salmonella Oranienburg are described, and the close bacteriologic similarity of this organism with S. suipestifer is considered.

The 2 latter infections were in 2 boys, 13 and 7 years old. One of the 6 former infections was in a girl, 3 years old. The 3 children recovered; 1 adult died.

GENGENBACH, Denver.

EXAMINATION OF 1,551 MEXICAN CHILDREN FOR OXYURIASIS BY THE GRAHAM METHOD. LUIS MAZZOTTI and ENRIQUETA QUINTANAR, Rev. d. Inst. salub. y enferm. trop. **4**:167 (June) 1943.

Of 1,551 children in Mexico between the ages of 2 and 13 years 41.8 per cent were found to be infected with oxyuriasis on one examination by the Graham method. Repeated examination showed 95 of 100 interns to be infected.

SANFORD, Chicago.

Diseases of Blood, Heart and Blood Vessels and Spleen

CONGENITAL SUBAORTIC STENOSIS, WITH DEFORMITY OF THE AORTIC VALVE. B. J. WALSH, H. V. CONNERTY and P. D. WHITE, Am. Heart J. **25**:837 (June) 1943.

A case of congenital subaortic stenosis with congenital deformation of the aortic valve is described; the patient was a woman who died, at the age of 29 years, of subacute bacterial endocarditis with a ruptured mycotic aneurysm of the aorta and cardiac tamponade. We believe that a correct diagnosis of congenital subaortic stenosis is possible in patients under the age of 20 years who show clinical evidence of aortic stenosis with a normal or nearly normal aortic second sound.

[FROM THE AUTHORS' SUMMARY.]

THE BLOOD PRESSURE OF ADOLESCENTS. HOMER E. LAWRENCE, New England J. Med. **228**:381 (March 25) 1943.

The incidence of hypertension among Selective Service registrants is said to be 3.02 per cent.

A certain proportion of students—9.5 per cent in this group—will show abnormally high blood pressures, as determined by the method of frequency distribution, after repeated observations. Most of these persons come from hypertensive families.

The frequency of abnormal responses to pressor tests among these adolescents with abnormal pressures tends to confirm the impression that many of them are in a prehypertensive stage.

There is need for a follow-up of subjects such as those described, in order to determine in later years whether high blood pressures and abnormal reactions to pressor tests during adolescence are truly indicative of a prehypertensive state.

GENGENBACH, Denver.

PRODUCTION OF RH ANTISERUM BY INOCULATION OF GUINEA PIGS WITH HUMAN ERYTHROCYTES. FRED W. GALLAGHER and LLOYD R. JONES, Proc. Soc. Exper. Biol. & Med. **53**:119 (June) 1943.

Red blood cells from a human subject with Rh-positive, group O, type MN blood were injected in various doses into guinea pigs over a period of three months. The presence of the Rh antigen in these cells was demonstrated by the fact that they agglutinated in several absorbed guinea pig antirhesus serums and in 6 human anti-Rh serums. Immune serum obtained in this manner when absorbed with group O, type MN, Rh-negative cells distinguished sharply between known Rh-positive and Rh-negative human erythrocytes of all blood groups. The authors believe these studies have greatly extended the possibility of producing an Rh antiserum useful in testing the red blood cells of human beings belonging to any blood group.

HANSEN, Minneapolis.

PRODUCTION OF HYPOPROTHROMBINEMIA AND HYPOCOAGULABILITY OF THE BLOOD WITH SALICYLATES. OVID O. MEYER and BERYL HOWARD, Proc. Soc. Exper. Biol. & Med. **53**:234 (June) 1943.

Study of the prothrombin time and the coagulation time was made for 31 adult human subjects who were receiving sodium salicylate or acetylsalicylic acid orally in daily doses of from 1.3 to 5.3 Gm. for periods of three to eleven days. The ingestion of either of the two substances resulted in a decrease in the prothrombin time of 1 to 4.5 seconds and in the coagulation time of variable but significant degrees depending on the dose used. When vitamin K was administered at the same time as the salicylates the development of the hypoprothrombinemia and the prolongation of the coagulation time were prevented. The authors speculate on the possibility that certain hemorrhagic symptoms seen in patients with rheumatic disease may be due to this effect of salicylates.

HANSEN, Minneapolis.

STUDIES ON PROTHROMBIN: IV. THE PROTHROMBINOPENIC EFFECT OF SALICYLATE IN MAN. SHEPARD SHAPIRO, MILTON H. REDISH and HAROLD A. CAMPBELL, Proc. Soc. Exper. Biol. & Med. **53**:251 (June) 1943.

Administration of sodium salicylate and acetylsalicylic acid to 27 adult subjects from 24 to 80 years of age induced prolongation of the prothrombin time. The effect was greatest in 6 patients with Laennec's cirrhosis of the liver. When vitamin K was given the decrease in prothrombin time did not occur except in a patient with cirrhosis of the liver. Dicoumarin administered with the salicylates produced a greater decrease in the prothrombin time. The action of salicylates seems to be identical with that of the anticoagulant dicoumarin, but the salicylates are less effective.

HANSEN, Minneapolis.

MICRO-METHOD FOR THE ESTIMATION OF THE SEDIMENTATION RATE OF RED CELLS. HILDA TROUGHT, Arch. Dis. Childhood **17**:136 (Sept.) 1942.

The advantage of this method is the small amount of blood (0.3 cc.) necessary for the test, which can easily be obtained by puncture of a capillary. Special blood pipets and tubes are used.

The following sedimentation rates were recorded: (*a*) for normal persons 0 to 5 mm. for half an hour and 0 to 10 mm. for one hour; (*b*) for moderately ill persons 8 mm. for half an hour and 14 mm. for one hour; (*c*) for gravely sick patients 20 mm. for half an hour and 30 mm. for one hour.

STUDIES IN THE ANAEMIAS OF INFANCY AND EARLY CHILDHOOD. H. S. BAAR and T. W. LLOYD, Arch. Dis. Childhood **18**:1 (March) 1943.

The authors summarize their extensive study as follows:

1. The properties of immature erythrocytes are discussed. The presence of substantia reticulofilamentosa is the only constant and reliable sign of immaturity of the red cell.

2. Erythrocytes are liberated from the bone marrow only in the reticulocyte stage.

3. Reticulocytes "cultured" in various mediums disappear, at first with a constant and then with a decreasing velocity.

4. The relation between the shape of the maturation curve and the kinetics of the reticulocytes' maturation is discussed. The decreasing velocity of the disappearance is due to an initiation of necrobiotic changes in the erythrocyte and does not represent a real decrease in the velocity of maturation. The maturation time is therefore obtained by extrapolation of the initial slope to the ordinate zero.

5. The average maturation time of normal reticulocytes is about seven hours. The maturation time in cases of reticulocytosis is usually longer, but there is no fixed relation between either the number of reticulocytes or the amount of reticular substance and the maturation time. The only condition in which a maturation time shorter than the normal was found is untreated pernicious anemia.

6. The daily regeneration rate is obtained by multiplying the percentage of reticulocytes by twenty-four and dividing this result by the maturation time in hours. One hundred divided by this figure gives the life span of erythrocytes in days if the number of red blood corpuscles is constant. From an average number of reticulocytes (0 to 7 per cent) and a maturation time of seven hours an average life span of forty-two days has been deduced.

7. The regeneration rate of hemoglobin is identical with that of erythrocytes as long as the color index remains unchanged. When such a change occurs a correction must be introduced into the formula.

KELLY, Milwaukee.

Diseases of Nose, Throat and Ear

PARAPHARYNGEAL ABSCESS IN CHILDREN. JUAN CARLOS OREGGIA, An. de oto-rino-laring. d. Uruguay **12**:210, 1942.

Oreggia presents 2 interesting cases of parapharyngeal abscess in children:

CASE 1.—A 3 year old boy stuck a glass tube into his mouth forty-eight hours before he was admitted to the hospital. The tube broke, and although several pieces were removed, a fragment about 2 cm. long remained in the right paratonsillar region. On admission to the hospital he was extremely toxic and pale and his temperature and pulse rate were elevated. The wound was explored in the hope of finding the fragment, but this search was unsuccessful. The wound was packed with iodoform gauze. Five days later an extensive hemorrhage occurred. It was controlled by tamponage, transfusion, the use of coagulants and other measures. Ligation of the carotid artery was advised, but the parents of the child refused consent to this operation.

The child continued to be toxic and to have an elevation of temperature, severe anemia and leukocytosis. Four days after the first hemorrhage a second occurred, which in a few seconds caused his death.

CASE 2.—A 19 month old infant was admitted to the hospital with a high temperature and marked debility of three days' duration. The symptoms continued, and on the twelfth day roentgen examination revealed a consolidation of the upper lobe of the right lung. Two weeks after admission the patient was found to have many lesions in the mouth. These were both ulcerative and necrotic and caused inflammatory swellings in the neck and in the floor of the mouth. These lesions progressed, causing marked necrosis of the left anterior pillar of the velum palatum. A culture from this region revealed a pure growth of an anaerobic streptococcus. A cervical gland was excised, but the pathologic report showed inflammatory adenitis. However, four days later the child died, and a final diagnosis of typhoid was made.

In discussing these cervical infections, the author lays emphasis on three common sites of involvement: (1) between the internal pterygoid and the styloglossus muscle, (2) along the course of the styloglossus muscle to invade the floor of the mouth and (3) along the course of the stylopharyngeus muscle to infiltrate the laryngeal operculum. In consequence one may observe either a submaxillary abscess, Ludwig's angina or laryngeal obstruction. Extension of the suppurative process along the large carotid vessels into the mediastinum can produce gangrene within the thorax, or passing along the larynx it may produce suppurative bronchopneumonia. At other times striking arterial necrosis may occur with fatal hemorrhage (as in case 1). Other sequelae are sepsis, gangrenous bronchopneumonia and asphyxia.

The author advocates early surgical drainage, ligation of the carotid artery in the presence of threatened or actual hemorrhage, and tracheotomy if asphyxia is imminent.

PERSKY, Philadelphia. [ARCH. OTOLARYNG.]

THROMBOPHLEBITIS OF THE CAVERNOUS SINUS. MARCOS COHN, Rev. de otorrinolaring. **2**:102 (Dec.) 1942.

Cohn presents a case of acute pharyngitis in a girl 3½ years old which became complicated by thrombosis of the cavernous sinus in two days. The child received intensive treatment with sulfapyridine and frequent small blood transfusions. She made a complete recovery.

PERSKY, Philadelphia. [ARCH. OTOLARYNG.]

THROMBOPHLEBITIS OF THE CAVERNOUS SINUS. ENRIQUE GRUNWALD S., Rev. de otorrinolaring. **2**:161 (March) 1943.

Grunwald, in a comprehensive review of observations on thrombophlebitis of the cavernous sinus, states that the involvement usually originates from an infection in the skin of the nasal vestibule, in the maxilla, in an eyelid or in the forehead. In its initial stage this infection appears as a small circumscribed abscess with limited, circumscribed thrombophlebitis of the surrounding small veins. If at this time the furuncle is either incised or traumatized, the infection may be disseminated through the small veins into the larger venous system, where it then may extend into the cavernous sinus and end fatally. Thus a small localized infection can be transformed into generalized septicemia.

The venous drainage into the cavernous sinus is usually effected through one of two vessels: (1) the superior ophthalmic vein, which receives blood from the forehead, the eyelids, the nose, the genionasal sulcus and the upper lip, and (2) the inferior ophthalmic vein, which drains the floor of the orbit, the maxilla, the inferior eyelids, the lacrimal sac, the nasolacrimal canal and the nasal fossae. These vessels traverse the orbit from before backward and unite to form the ophthalmic vein, which passes through the sphenoid fissure and empties into the cavernous sinus.

There are three routes by which an infection can reach the cavernous sinus. The first is the anterior route, which is by way of the ophthalmic vein as already described. A suppurative process of the frontal sinuses, a hematoma of the septum or an infection in the nasal chamber can follow this route and involve the cavernous sinus. The second is a lateral route, by way of the veins of the foramen ovale, which receive blood from the pterygoid venous plexus. This plexus drains the buccal mucosa, the dental alveolus, the pharynx and the tonsils. The third is the posterior route, by way of the superior and inferior petrosal sinuses. These sinuses have communication with the lateral sinus and the internal jugular vein, respectively. This relation between the cavernous sinus and the venous circulation of the temporal bone and also of the superior part of the neck explains a number of cases of cavernous sinus thrombosis which took origin in mastoiditis or cervical adenitis.

The symptoms of thrombophlebitis of the cavernous sinus are due to sudden blockage of the return circulation with secondary infiltration of the orbital tissues. The most important symptoms are palpebral edema, conjunctival ecchymosis and exophthalmos. These symptoms are usually bilateral. There are also ophthalmoplegia, loss of vision, signs of generalized septicemia, such as pyrexia and chills, and finally symptoms of complicating meningitis.

The prognosis is always extremely grave. Prior to the advent of sulfonamide compounds the mortality was 100 per cent. Death usually ensued four to ten days after the onset of symptoms. Now, with the intensive use of the sulfonamide drugs, an occasional cure has been reported in the literature. Grunwald observed 3 cures and 2 deaths recently.

He summarizes the various surgical technics that have been advocated. These are all of doubtful value. He stresses the importance of prophylaxis.

In conclusion Grunwald outlines the therapy as essentially chemotherapy, blood transfusions, the use of serums and vaccines, lumbar punctures, the administration of cardiac stimulants and sedation.

PERSKY, Philadelphia. [ARCH. OTOLARYNG.]

Diseases of Lungs, Pleura and Mediastinum

BLOOD PRESSURE FLUCTUATIONS IN BRONCHIAL ASTHMA. HOWARD OSGOOD, J. Lab. & Clin. Med. **28**:927 (May) 1943.

Wide fluctuations of the systolic blood pressure, correlated with the respiratory cycle, are constantly present in patients with bronchial asthma. The high point of each fluctuation occurs during expiration; the low point, during inspiration. The amplitude of the fluctuations parallels closely the severity of the asthma.

WILKINSON, Galveston, Texas.

A CLINICAL AND BACTERIOLOGICAL SURVEY OF PNEUMONIA IN CHILDHOOD. ESTHER HENDRY, Arch. Dis. Childhood, **17**:111 (Sept.) 1942.

One hundred and eighty-six cases of pneumonia were investigated. One hundred and twenty-three, or 66.4 per cent, of the patients were children under 2 years of age.

The mortality rate was low. For children under 2 years it was 19 per cent and for those over 2 years 3 per cent. Probably treatment with sulfapyridine was responsible for the low rate.

All the recognized types of the pneumococci save types XXVIII, XXXII and XXXIII were found on one or more occasions. Types XIX and VI were the ones most frequently encountered. They accounted for 38.3 per cent of the cases of pneumonia from which a pneumococcus was isolated.

Types 1 and 2 occurred only rarely in children under 2 years of age. Of the two types most frequently found (types VI and XIX) the former was evenly distributed between children under and over 2 years of age; the latter was relatively more frequently found in children over 2 years of age.

It was rare to find the causal pneumococcus persisting in the respiratory tract after the acute stage of the illness was over.

KELLY, Milwaukee.

Diseases of the Gastrointestinal Tract, Liver and Peritoneum

HOSPITAL DIARRHOEA. PHILIP EVANS, Arch. Dis. Childhood **17**:130 (Sept.) 1942.

Epidemics of diarrhea are all too common in children's hospitals, and epidemiologic classification can

point the way to prophylaxis. In one hospital the outbreaks could be divided into cases of "food poisoning," of Sonne dysentery (which is difficult to control for a variety of reasons) and of diarrhea affecting infants but probably due to infections which attack the respiratory tracts of older children. In addition, sporadic attacks occurred in malnourished infants, who often had parenteral infection. Many of these sporadic attacks were fatal.

KELLY, Milwaukee.

INTESTINAL INVAGINATION IN INFANCY. JOAO F. FORTES, Rev. méd munic. **5**:359 (April-June) 1943.

The author is a radiologist and takes up the subject of intussusception from that standpoint. He states the belief that a barium enema is indispensable for diagnosis, giving several examples to illustrate. The pictures are excellent.

SANFORD, Chicago.

HERNIAS AND EVENTRATIONS OF THE DIAPHRAGM. MAURICIO J. L. ROCHA and J. DE CASTRO BARBOSA, Rev. méd. munic. **5**:397 (April-June) 1943.

The authors review this subject from the results of twenty-four observations and present a study of the differential roentgen diagnosis. They state the belief that clinical diagnosis should be assisted by roentgen examination. Excellent roentgenograms are shown.

SANFORD, Chicago.

Nervous Diseases

MULTIPLE SCLEROSIS AND ENCEPHALOMYELITIS. TRACY J. PUTNAM, Bull. New York Acad. Med. **19**:301 (May) 1943.

Pathologically multiple sclerosis is characterized by the existence of glial cells scattered throughout the nervous system. Gliosis is secondary to damage to the tissues. In the author's opinion this is a chronic form of a demyelinating process and includes the types known as postinfectious encephalitis, Schilder's disease, diffuse sclerosis, neuromyelitis optica and transverse myelitis.

The various phases of the acute and the chronic nature of the demyelinating processes and the causation, the prognosis and the therapy of these disorders are presented clearly. The paper deserves careful study in the original.

JAHR, Omaha.

PUBERTAS PRAECOX IN A FEMALE INFANT CAUSED BY VENTRICULAR CYST. DAVID J. FLICKER, J. Nerv. & Ment. Dis. **98**:42 (July) 1943.

Flicker adds a fourth confirmed case to the 3 previously reported instances of pubertas praecox in females. The case was that of a girl who was first seen at the age of 3 years because of precocious sexual development and failing eyesight. In addition, there were spastic hemiplegia and hyperalgesia on the right side, primary atrophy of both optic nerves and nystagmus on looking to the right. Encephalographic examination revealed enlargement of both lateral ventricles, the left being the larger; ventriculographic studies showed a small, circumscribed spherical mass in the region of the pineal gland. A frontoparietotemporal flap was laid down, and a cyst of the third ventricle was encountered.

CHODOFF, Langley Feld, Va.
[ARCH. NEUROL. & PSYCHIAT.]

EFFECT ON THE ELECTRICAL ACTIVITY OF THE CORTEX OF CERTAIN DEPRESSANT AND STIMULANT DRUGS—BARBITURATES, MORPHINE, CAFFEINE, BENZEDRINE AND ADRENALIN. FREDERIC A. GIBBS and GEORGE L. MALTBY, J. Pharmacol. & Exper. Therap. **78**:1 (May) 1943.

After a brief revivew of the important facts about the electrical activity of the cortex, the authors describe in detail the results of their study of the action of drugs on 6 men free of known cerebral abnormalities. The summary in part follows:

"(1) Phenobarbital, pentothal and morphine caused a shift in frequency to the slow side comparable to that occurring in sleep.

"(2) Caffeine, benzedrine and adrenalin caused a shift in frequency to the fast side comparable to that occurring with attention. . . .

"(4) Of the drugs studied, the one (pentothal) which produced the greatest clinical evidence of depression, caused the greatest shift to the slow side, and the one (adrenalin) which produced the greatest evidence of stimulation, caused the greatest shift to the fast side."

PILCHER, Cleveland.

MISARTICULATION AND DIADOKOKINESIS IN THE SPASTIC PARALYTIC. HARRY J. HELTMAN and GEORGIANA M. PEACHER, J. Speech Disorders **8**:137 (June) 1943.

The speech of 102 persons with spastic paralysis was compared with that of 159 nonspastic persons with defective speech. 1. All sounds were misarticulated more frequently by the subjects with septic diseases. 2. Linguarugal sounds were most difficult for those with spasticity. 3. Most dyslalia was found in persons with spastic athetotic quadriplegia. 4. There were no sex differences. 5. Dysphonias were rare in the athetotic patients, while half of the spastic patients presented dysphonias. 6. The incidence of stuttering was the same in both groups. 7. Four patients with spasticity were hard of hearing, and 2 were deaf. 8. Diadokokinesis was slower in the presence of spastic paralysis. 9. The diadokokinetic rate and the number of misarticulations were negatively correlated. 10. Rates of lip and tongue movements increased with sonants.

PALMER, Wichita, Kan.

THE SPASTIC SITUATION. STELLA MCKIBBEN, J. Speech Disorders **8**:147 (June) 1943.

A great part of the difficulty in treating spastic paralysis is the misunderstanding, by physicians and parents, of the psychologic aspects of the condition.

PALMER, Wichita, Kan.

CONGENITAL NARROWING OF THE LUMBOSACRAL SPACE. THEODORE H. VINKE and EDGAR H. WHITE, Surg., Gynec. & Obst. **76**:551 (May) 1943.

Narrowing of the lumbosacral intervertebral space, as seen in roentgenograms, has recently been interpreted as the result usually of herniation of the nucleus pulposus. Vinke and White believe that congenital narrowing of the disk in this interspace occurs more frequently than is commonly supposed. The roentgenograms of 300 children between the ages of 5 and 15 years were reviewed, none of the children being included in the study for whom there was evidence of fracture, infection or trauma or whose roentgenogram was unsatisfactory. Any narrowing of the interspace in this series must, they felt, be of congenital origin. Three cases of this

anomaly were found, the narrowing in all being associated with lumbarization or sacralization. Other observers had previously noted associated narrowing of the interspace with congenital anomalies of the lower part of the back, particularly sacralization. The cases of 6 adults with pain in the lower part of the back, without sciatica and with an appreciably narrowed lumbosacral interspace are reported. In these 6 patients none of the signs suggested ruptured intervertebral disk. All responded excellently to conservative management.

The authors conclude that in questionable cases a narrowed lumbosacral interspace should invite close observation for other congenital anomalies before it is used as supportive evidence in favor of a herniated disk.

SHENKIN, Philadelphia.
[ARCH. NEUROL. & PSYCHIAT.]

OLIGODENDROGLIOMA IN AN INFANT OF EIGHT MONTHS. ROBERT R. HUGHES AND EDWARD C. R. COUPER, Arch. Dis. Childhood **17**:147 (Sept.) 1942.

A case of a midline supratentorial tumor with an oligodendrogliomatous center and a medulloblastomatous periphery occurring in an infant of 8 months and presenting a rare combination of clinical and pathologic features is described. KELLY, Milwaukee.

Diseases of the Muscles, Bones, Joints and Lymph Glands

ARTHROGRYPOSIS MULTIPLEX CONGENITA. MIRIAM KATZEFF, Arch. Surg. **46**:673 (May) 1943.

Various other names, such as "amyoplasia congenita" and "myostrophia congenita," in addition to "arthrogryposis multiplex congenita," have been given to congenital contractures of the joints. The cause of this condition is not clear, but it is supposed that the deformities result from fatty degeneration of muscles occurring during intrauterine life. The author observed 18 patients with such contractures, ranging in age from 5 to 10 years. In cases of arthrogryposis the extremities present a unique appearance. They lack the usual anatomic contours, having instead a stuffed, sausage-like appearance. Very little muscle is palpable. The structures overlying the joints feel thickened and contracted. These gross abnormalities are symmetric, distinctive and readily recognizable. Treatment consisted of manipulations, supports and surgical correction. Excellent results are reported.

KAISER, Rochester, N. Y.

POLYOSTOTIC FIBROUS DYSPLASIA: REVIEW OF THE LITERATURE WITH TWO ADDITIONAL CASES. NATHAN JAMES FURST and ROBERT SHAPIRO, Radiology **40**: 501 (May) 1943.

The authors state that it is not unlikely that some of von Recklinghausen's original cases may have been instances of polyostotic fibrous dysplasia, the disease entity first described in this country by Albright (1937) and Lichtenstein (1938). Other cases seem to have been reported as instances of "osteitis fibrosa cystica congenita," "bone dystrophy with characteristics of leontiasis ossea," "osteitis deformans," "xanthomatosis generalisata ossium," "unilateral von Recklinghausen's disease of bone" and "juvenile Paget's disease."

The cause has not been established, but it is not impossible that some as yet undetermined disturbance of the parathyrotropic hormone of the anterior pituitary might account for the disease.

The blood elements are usually within the normal limits, but serum phosphatase may vary considerably. The basal metabolic rate and the calcium metabolism are normal.

This disease may be suspected clinically but cannot be established with certainty without roentgenograms. The author summarizes the roentgenologic findings as follows:

"1. The skeletal involvement has some tendency to be unilateral in distribution, but bilateral lesions are not uncommon.

"2. Contrary to the findings in hyperparathyroidism, no generalized decalcification of the bones is present. The lesions are spotty in distribution, consisting of multiple localized areas of diseased bone with normal osseous tissue between.

"3. The characteristic lesions are areas of rarefaction resembling bone cysts. These vary considerably in size and shape, and may occur in flat as well as in long bones. The borders of the fibrocystic-like lesions may be sharply defined or gradually fade into the surrounding normal bone tissue. The lesions are not true cysts. The x-ray appearance is due to the replacement of the bone by the fibrous tissue.

"4. Along with the cyst-like changes, areas of increased density are observed. These vary in extent and may be so pronounced as to result in almost complete obliteration of the medullary canal. Such lesions are particularly prone to occur in the skull, especially at the base, in the region of the floor of the anterior fossa.

"5. There is marked thinning of the cortex, along with broadening or expansion of the involved bones. The cortical outline usually remains intact but may occasionally be broken, even in the absence of a pathological fracture.

"6. Periosteal reaction rarely occurs except at the site of fracture.

"7. Advanced bone age and early epiphyseal union may be present.

"8. Frequently, the epiphyses remain intact in the face of diffuse diaphyseal involvement.

"9. Various secondary deformities of the involved bones may be present, e. g., coxa vara, bowing of the femur and tibia.

"10. Pathological fractures are not uncommon.

"11. The skull is a frequent site of the disease process and may be involved in various ways. (a) Irregular dense areas along with the fibrocystic-like involvement may be present, producing a picture not unlike Paget's disease. (b) Extensive sharply demarcated areas of rarefaction may occur, simulating xanthomatosis to some extent. (c) The bones of the face and orbit may be involved in a dense, fibrotic process resembling leontiasis ossea. (d) The mastoid cells and paranasal sinuses may be obliterated by the dense fibrous deposits, and the extension of the disease process into the bones of the face and orbit may lead to facial asymmetry and ocular proptosis."

This condition must be differentiated from hyperparathyroidism, regional fibrocystic disease, dyschondroplasia (skeletal enchondromatosis), osteitis deformans (Paget's disease of bone), leontiasis ossea, Hand-Schüller-Christian disease, bone cyst and giant cell tumor.

If fractures can be avoided, the progress is good, as the disease is self limited. The condition does not improve, but it becomes stationary and new lesions do not

develop. Local radiation therapy has proved to be of some benefit. The patient should be warned against undue trauma and severe exercise because of the tendency for spontaneous fracture to occur.

The cases of 2 patients, a boy aged 15 and a girl aged 17, are reported in detail. ANSPACH, Chicago.

STUDIES IN THE DEPOSITION OF LEAD IN BONE: I. CALCIFICATION AND LEAD DEPOSITION. F. R. BARRETT, M. J. Australia **1**:433 (May 15) 1943.

In experiments with rats, Barret notes that lead is deposited at those sites where the new calcium is also being deposited. Lead exhibits the same relative activities at the calcifying sites as calcium, the least activity in the subperiosteum of the shaft and the greatest at he distal diaphysial plate. The simultaneous deposition of lead and removal of calcium found by other workers are shown to be due to accelerated decalcification of the compact bone, in which there is no lead, with simultaneous calcification and deposition of lead at the epiphyses.

GONCE, Madison, Wis.

COLLAPSED INTERVERTEBRAL DISC FOLLOWING LUMBAR PUNCTURE. B. J. HUSSEY, Proc. Roy. Soc. Med. **36**:379 (May) 1943.

In May 1942 a girl aged 4 years was admitted to the hospital with a tentative diagnosis of meningitis and with a history of sudden onset of vomiting and delirium. Lumbar puncture was performed, and the cerebrospinal fluid was found to be normal. No definite diagnosis was made, but in six days the child was discharged from the hospital apparently quite fit. Four days later she complained of headache and pains in the legs and was mentally upset. Eight days after her discharge from the hospital she was readmitted. This time her gait was awkward, and she suffered pain in her back when she walked. There was a suppurating wound at the site of the puncture, in the space between the second and third lumbar vertebrae. No signs of abnormal conditions were found in the central nervous system. Roentgen examination of the spinal column showed that the space between the spinous processes of the second and third lumbar vertebrae was greatly diminished. The spinal column was immobilized in a plaster jacket for three months after which gradually increasing movement was allowed and later graduated exercises were started. The child made a complete recovery.

WILLIAMSON, New Orleans.

Skin Diseases; Allergy

MOLLUSCUM CONTAGIOSUM OF THE EYE. L. A. JULIANELLE and W. M. JAMES, Am. J. Ophth. **26**:565 (June) 1943.

The authors find that molluscum contagiosum of the eye is an uncommon condition of the lids characterized by persistent conjunctivitis and sometimes accompanied by keratitis. The clinical appearance may be deceiving because of its similarity to marginal chalazia, milia and warts, but diagnosis by histologic examination is infallible. In any case all nodules should be removed. Treatment in all 5 cases reported consisted of resection followed by mild irrigation; recurrence did not take place when the nodules were completely removed. The disease, unlike others of virus origin, is of low infectivity, in support of which the authors cite a number of reasons.

WIEDER, Milwaukee.
[ARCH. DERMAT. & SYPH.]

Surgery and Orthopedics

REDUCTION OF FLUID LOSS FROM DAMAGED (BURNED) TISSUES BY A BARBITURATE. HENRY K. BEECHER and JANE D. MCCARRELL, J. Pharmacol. & Exper. Therap. **78**:39 (May) 1943.

The authors call attention to the damaging effect of the loss of fluid containing large amounts of protein from tissues after severe burns, and they report the results of the use of a barbiturate (pentobarbital sodium) in experimentally produced burns. After producing localized insensitivity to pain, by destruction of part of the cerebral cortex (under procaine anesthesia) in chickens and by section of the cord in rabbits and a few young pigs, the investigators dipped the anesthetized parts into hot water for brief periods. Considerably less fluid was lost from the burned areas in the animals that had received the barbiturate shortly after the burns than in control animals. Pentobarbital sodium reduced the capillary congestion of the mucosa which results from burning of the intestine. The authors discuss the mechanism of the action of the drug. "The degree of sedation was about the same as that an average man would get from the oral administration of 0.2 to 0.25 grams of the agent."

PILCHER, Cleveland.

ACROLEIN AND SHOCK: POSSIBLE RELATIONSHIP OF LIPOID BREAKDOWN PRODUCTS TO SHOCK ASSOCIATED WITH BURNS. GEORGE F. KAMEN, Proc. Soc. Exper. Biol. & Med. **52**:363 (April) 1943.

Acrolein diluted 1:10 with isotonic solution of sodium chloride was injected, by various parenteral routes, into dogs, cats and one rabbit. All the animals presented the classic clinical picture of shock, with hemoconcentration, falling blood pressure and terminal pulmonary edema. Postmortem examination revealed visceral congestion, even to the point of capillary hemorrhage, especially in the mucosa of the stomach and duodenum, and pulmonary edema. The gross and microscopic appearance of the tissues was consistent with the evidence of shock. Control animals, maintained under ether anesthesia, showed an average hemoconcentration of less than 5 per cent (in the animals treated with acrolein the hemoconcentration was greater), and the tissues of these animals were normal.

HANSEN, Minneapolis.

CONGENITAL DISLOCATION OF HIP. HARRY PLATT, Brit. J. Surg. **30**:291 (April) 1943.

Manipulation and fixation in a plaster cast is the method of choice for treatment of congenital dislocation of the hip except in young infants in whom dislocation is discovered before they walk. Gentle abduction by means of the divaricator gives them complete reduction after several weeks or months in 60 to 90 per cent of the cases.

Several comprehensive surveys on late results of manipulative reduction are mentioned, and the author analyzes results in 104 of his patients reexamined five to twenty-five years after manipulative treatment.

The causes of failure in the results of manipulative treatment are discussed, and recommendations are given for treatment of residual subluxation after reduction.

Indications for treatment by open reduction are cited, and illustrations demonstrate recent results in some of the author's cases in his series of 42 in which this method of treatment was used.

BRICK, Toronto, Canada.

OBSERVATIONS ON C T A·B (CETAVLON): ITS USE IN SURGERY. ROBERT WILLIAMS, J. McK. DUNCAN, BARBARA CLAYTON-COOPER and ELLEN M. MILES, Lancet **1**:522 (April 24) 1943.

One per cent cetyl trimethyl ammonium bromide proved to be an excellent agent for cleansing surfaces of organic matter and had considerable antiseptic powers on already clean surfaces. The authors recommend it both for cleaning and for sterilization of utensils and instruments and for cleansing of wounds and of the skin surrounding wounds.

Cutaneous reactions occur in a small percentage of sensitive persons. LANGEMANN, New York.

Teeth and Dentistry

THE CARIES-FLUORINE HYPOTHESIS AND A SUGGESTED STUDY TO TEST ITS APPLICATION. DAVID BERNARD, Pub. Health Rep. **58**:857 (June 4) 1943.

All of the early studies on fluorine were concerned with toxic doses and the resultant mottling of the enamel. The chief practical problem to be solved after these observations was the elimination of fluorine from the public drinking water. As these studies progressed, the relationship of a low incidence of caries to the presence of a small amount of fluorine in the drinking water became evident, and this discovery opened up a field of tremendous importance to those in public health work who are trying to solve the problem of dental caries. With investigations to date indicating the apparent safety of small doses, such as 1 part per million of fluorine in water, further experimentation, with this threshold dose or less, is warranted in order to test the efficacy and practicability of using this element universally, under strict control, to reduce the incidence and ravages of dental caries. SANFORD, Chicago.

SOME DISORDERS OF THE DENTITION PERIOD. DONALD PATERSON, Practitioner **150**:225 (April) 1943.

The author emphasizes that, as dentition is a natural process, the practitioner should exclude organic disease with the greatest care before he attributes symptoms of importance to teething itself. He lists as the common diseases occurring during the period of dentition pyelitis, celiac disease, nasopharyngitis, otitis media, meningitis, miliary tuberculosis, stomatitis, gingivitis and erythredema. Faulty management of the period of teething may play a definite part in the production of sleeplessness, loss of appetite, vomiting or diarrhea, with consequent failure to thrive and various rashes. THELANDER, San Francisco.

TREATMENT OF CARIES IN CHILDREN WITH SILVER NITRATE. GUSTAVO A. CHIAPPORI, Rev. de hig. y med. esc. **2**:22, 1943.

Because of the importance of prophylactic odontotomy the author gives an account of Kellog's technic for the treatment of incipient caries in the proximal faces of temporary molars and permanent premolars or molars visible only by roentgen examination.

He arrives at the following conclusions:

1. Silver precipitates in the presence of the organic substances of the tooth and penetrates the canaliculi of the dentine, reaching the interprismatic spaces of the enamel, but it does not harm the pulp.

2. The Kellog technic restricts to a minimum the destruction of dental tissue and preserves the integrity of the margin.

3. The rapidity with which this operation is performed is an advantage, since it is not always easy to do precise and delicate work on children.

4. The impregnation of the whole affected zone with silver can be effected in two weeks.

[FROM THE AUTHOR'S SUMMARY.]

DENTAL SERVICES FOR SCHOOL CHILDREN OF THE INTERIOR: IDEAS ON THE ORGANIZATION AND FUNCTION OF DENTISTRY AMONG SCHOOL CHILDREN. LOUISA I. SALMAIN, Rev. de hig. y med. esc. **2**:71, 1943.

Dental services for children can be divided into three groups based on the three stages of development of the two dentitions: the infantile period (up to the age of 3 years), the preschool period (3 to 5 years) and the school period (5 to 14 years).

About 80 per cent of the school children in Argentina have dental decay; that is, about 1,200,000 children need dental assistance provided by the state.

In addition to the measures instituted by each province with the means at its disposal, a national law (12,558) provides for dental services for these children throughout the country, the services to be rendered in the schools, centralization of the dental work thus being avoided.

Regulations made by the National Board of School Aid (Comision Nacional de Ayuda Escolar) provide for three types of dental services "fixed" for the cities, "motorized" or "by ambulance" for the zones provided with good roads and "portable" for the schools that are scattered in the country.

The "work plan" stipulates that the services rendered should be of types which benefit the greatest number of children, such as attention to early or incipient caries, and should favor the education of parents, teachers and children in sanitation and hygiene simultaneously with the treatment of the child.

This task is a difficult one in Argentina, owing to the great distances between schools and the frequent precarious condition of the roads.

The dentist's skill and social spirit, together with his technical specialization, will contribute to success in a social work which is precise, manual and difficult.

"Portable" dental services will be, by the simplicity of their equipment and their facility of transportation, the most efficient and practical elements to fulfil the two prime objects of the school dental service. Early treatment of caries in the permanent dentition and education in dental hygiene.

[FROM THE AUTHOR'S SUMMARY.]

Miscellaneous

SEVERE INJURY TO KIDNEYS AND BRAIN FOLLOWING SULFATHIAZOLE ADMINISTRATION: HIGH SERUM SODIUM AND CHLORIDE LEVELS AND PERSISTENT CEREBRAL DAMAGE. JOHN A. LUETSCHER JR. and SAM S. BLACKMAN JR., Ann. Int. Med. **18**:741 (May) 1943.

Intoxication from sulfathiazole may be complicated by severe renal damage resulting in unusual concentrations of sodium chloride in the blood serum, possibly as the result of thrombi in the interlobular veins and arteries.

In such cases among those described by the authors, evidences of cerebral damage were present and persistent and recovery was slow and incomplete.

READING, Galveston, Texas.

FEVER THERAPY. GORDON B. TAYLOE, Ann. Int. Med. **18**:968 (June) 1943.

Fever therapy in combination with chemotherapy offers the best method of treating gonococcic infection, neurosyphilis and dementia paralytica. This form of therapy is a valuable adjunct in the treatment of chorea, infectious arthritis and brucellosis.

READING, Galveston, Texas.

SULFANILAMIDE BACTERIOSTASIS IN THE PRESENCE OF MERCURIC CHLORIDE AND *p*-AMINOBENZOIC ACID. CARL LAMANNA and IRVING M. SHAPIRO, J. Bact. **45**:385 (April) 1943.

The authors studied the influence of paraaminobenzoic acid on the growth-stimulating concentration of sulfanilamide and the mutual antagonism of mercury bichloride and sulfanilamide. A strain of Escherichia coli was used which gave abundant growth on the synthetic medium of MacLeod. Their results revealed that in the presence of paraaminobenzoic acid the growth-stimulating concentration of sulfanilamide is increased. The antisulfanilamide activity of paraaminobenzoic acid was not dependent on its stimulating growth.

Mixtures of various concentrations of sulfanilamide and mercury bichloride produced the following interesting effects on growth:

1. Mixtures of both in stimulating concentration were toxic.

2. Sulfanilamide antagonized mercury bichloride bacteriostasis, and mercury bichloride, sulfanilamide bacteriostasis.

3. Addition of some noninhibitory concentrations of mercury bichloride enhanced sulfanilamide toxicity.

4. Increased additive inhibition was observed in certain mixtures of toxic concentrations of the drugs in the blood.

STOESSER, Minneapolis.

THE ABSORPTION, EXCRETION AND DISTRIBUTION OF PENICILLIN. CHARLES H. RAMMELKAMP and CHESTER S. KEEFER, J. Clin. Investigation **22**:425 (May) 1943.

Data are presented concerning the blood concentration and urinary excretion of penicillin after the administration of 5,000 to 40,000 Florey units by several routes.

Intravenous injection of penicillin resulted in high initial concentration in the blood plasma, which was followed by an abrupt fall. Traces of penicillin were found in the blood for thirty to two hundred and ten minutes after the injection, the length of time depending on the amount administered. The sharp fall noted in the serum concentration immediately after injection was associated with an increased excretion in the urine. The average excretion after intravenous injection was 58 per cent of the administered dose.

Penicillin was rapidly absorbed when given intramuscularly and slowly absorbed after subcutaneous injections. Excretion in the urine was rapid following intramuscular injections and delayed after subcutaneous injections.

Absorption from the body cavities was delayed, and this was reflected in the slow excretion of penicillin by the kidneys. The total amount found in the urine was somewhat lower than that obtained following intravenous injection. Fluid aspirated from the pleural and joint cavities, twenty-two and thirteen hours after the injection, showed appreciable amounts of penicillin remaining.

Administration of penicillin by enteral routes showed that absorption from the duodenum was rapid, whereas oral and rectal doses were poorly absorbed. These findings may be explained by the inactivating effect on penicillin of acid and Escherichia coli. After oral, intraduodenal and rectal administration, the average amount excreted in the urine was extremely small.

In the presence of renal failure, penicillin was not excreted rapidly, and as a result high concentrations were maintained in the blood stream after intravenous injections.

Studies on the distribution of penicillin showed that the substance failed to penetrate the red cells in significant amounts. In general, the average concentration found in the erythrocytes was less than 10 per cent of the concentration in the plasma. No penicillin was found in the spinal fluid, saliva or tears in subjects receiving it intravenously.

[AUTHORS' SUMMARY.]

LESIONS IN THE TISSUES OF THE BODY FOLLOWING SULFONAMIDE THERAPY. H. J. SCHATTENBERG and W. H. HARRIS JR., J. Lab. & Clin. Med. **28**:671 (March) 1943.

The authors point out that any organ or tissue of the body may be affected through the toxic action of sulfonamide compounds. The immediate effects of these drugs on the skin, liver, kidney and nervous system is well known. "It is not possible at this time to say what residual effects may be noted in the myocardium, liver or other organs years later. Might such changes lead to chronic myocarditis or cirrhosis of the liver? Might they lead to bizarre blood dyscrasia?" A plea is made for greater caution in the use of these drugs.

WILKINSON, Galveston, Texas.

THE EFFECT OF CONTINUED SULFANILAMIDE INGESTION ON THE ACID-BASE EQUILIBRIUM OF THE DOG. ALFRED H. FREE, DONALD E. BOWMAN and DEAN F. DAVIES, J. Lab. & Clin. Med. **28**:1109 (June) 1943.

The studies reported indicate that with the continued administration of sulfanilamide and the maintenance of therapeutic levels of sulfanilamide in the blood there are no great changes in the acid-base equilibrium. Small decreases in serum bicarbonate were observed, but there was no appreciable alteration in the p_H of the serum. Administration of sodium citrate along with the sulfanilamide prevented any decrease in serum bicarbonate.

WILKINSON, Galveston, Texas.

EVALUATION OF THE DANGERS OF REPEATED ADMINISTRATION OF SULFADIAZINE AND SULFATHIAZOLE IN CHILDREN. HERBERT W. FINK and JAMES L. WILSON, J. Pediat. **22**:513 (May) 1943.

Many instances of sensitization to sulfathiazole and sulfadiazine with serious reactions on a second administration of the drug have been reported, particularly in adults. Fink and Wilson made a study of 177 children who had previously received sulfonamide drugs, 86 having been given sulfathiazole and 91 sulfadiazine. The interval between courses of the drug was over

seven days for all children. This factor is important, inasmuch as nine to twelve days must elapse before sensitization occurs. Seven of the 177 children had a febrile reaction during the second administration, 3 from sulfathiazole and 4 from sulfadiazine; none showed the typical immediate febrile response characteristic of sensitization to a drug. However, in a separate study, of 5 children who had reactions during the first course of drug therapy 3 had an immediate febrile response and an associated rash within eight hours after the second course. The authors conclude that sensitization to the sulfonamide drugs is uncommon in children, but they warn that the drug must be given with caution the second time if a reaction has occurred with the first administration.

STETTENBENZ, Buffalo.

SULFAPYRIDINE BACTERIOSTASIS OF LACTOBACILLUS ARABINOSUS AND ITS COUNTERACTION. L. J. TEPLY, A. E. AXELROD and C. A. ELVEHJEM, J. Pharmacol. & Exper. Therap. **77**:207 (March) 1943.

Numerous papers are appearing on the interaction of bacteria and sulfonamide drugs. This one deals with Lactobacillus arabinosis 17-5, an organism for which nicotinic acid is a distinct essential growth factor. It was found that sulfapyridine prevented growth of this organism, but that its activity was completely counteracted by paraaminobenzoic acid or high levels of nicotinic acid and by fresh and dried liver. "Sulfaguanidine and sulfasuxidine are less potent than sulfapyridine and are completely counteracted by p-amino-benzoic acid."

PILCHER, Cleveland.

PREVENTION OF CRYSTALLURIA DURING SULFADIAZINE THERAPY: EXPERIMENTAL AND CLINICAL STUDIES. D. ROURKE GILLIGAN, SOLOMON GARB and NORMAN PLUMMER, Proc. Soc. Exper. Biol. & Med. **52**:248 (March) 1943.

The solubilities of sulfadiazine and acetylsulfadiazine in urine and in solutions of citrate and phosphate buffers were found to increase with increase of p_H from 5.2 to 7.6. In clinical studies 27 per cent of 172 patients with acid urine had crystalluria after sulfadiazine therapy, whereas only 1.4 per cent of 147 patients with neutral or alkaline urine were found to have sulfadiazine crystalluria. The administration of sodium bicarbonate is effective in maintaining a neutral or alkaline urine, and it was found to prevent crystalluria following the use of sulfadiazine. The importance of proper fluid intake is also stressed by the authors.

HANSEN, Minneapolis.

SULFAPYRAZINE: ITS ACTIVITY AGAINST EXPERIMENTAL INFECTIONS WITH BETA HEMOLYTIC STREPTOCOCCI AS COMPARED WITH THAT OF SULFADIAZINE, SULFATHIAZOLE, SULFAPYRIDINE AND SULFANILAMIDE. L. H. SCHMIDT and CLARA L. SESLER, J. Pharmacol. & Exper. Therap. **77**:277 (March) 1943.

The drugs were tested on white mice infected with one of the six strains of the organism cited. Single large doses or repeated small doses of sulfapyrazine were similar in effectiveness to sulfadiazine but more effective than the other drugs. With the smallest doses, sulfapyrazine and sulfadiazine showed higher concentrations in the blood than the other drugs. The blood concentration was maintained at a uniform level longer with sulfapyrazine than with the other drugs, but it was higher with sulfathiazole than with any of the other four drugs. The results suggest that in streptococcic infections sulfathiazole and sulfapyrazine are more effective because of their more uniformly high blood concentrations. With similar concentrations in the blood the activities of all seemed to be the same.

PILCHER, Cleveland.

THE CHEMOTHERAPEUTIC EFFECT OF ESTERS OF PENICILLIN. KARL MEYER, GLADYS L. HOBBY and MARTIN H. DAWSON, Proc. Soc. Exper. Biol. & Med. **53**:100 (June) 1943.

Ethyl and n-butyl esters of penicillin, although previously found to be ineffective bacteriostatically in vitro, were found to protect mice infected with group A hemolytic streptococci. These esters were active when administered orally as well as subcutaneously. In addition to being stable these esters are not destroyed at the p_H of the stomach. Ten times greater amounts were required by the oral than by the subcutaneous route. The toxicity of the esters is two to three times that of penicillin, but the range between the chemotherapeutic and the toxic levels although rather close in the case of the oral route, is sufficiently safe for the satisfactory use of these esters of penicillin.

HANSEN, Minneapolis.

RESISTANCE TO DISEASES IN CHILDHOOD. B. B. JONES, South. M. J. **36**:442 (June) 1943.

The author advances the idea that repeated allergic reactions and psychic trauma are related etiologically to diseases not commonly associated with such factors. He presents a large amount of interesting case material to prove his point.

Children with certain constitutional heritages seem to be more liable to these manifestations than those with essentially normal constitutional makeup.

SCHLUTZ, Chicago.

GENERAL AND LOCAL ADMINISTRATION OF PENICILLIN. M. E. FLOREY and H. W. FLOREY, Lancet **1**:387 (March 27) 1943.

Of 15 seriously ill patients treated with penicillin by mouth or by intravenous or intramuscular injection, 10 had a staphylococcic infection, 1 a streptococcic meningitis resistant to sulfonamide compounds, 3 infection with Actinomyces or Streptothrix plus an anaerobic streptococcus and 1 a subacute bacterial endocarditis due to Streptococcus viridans.

From this series the authors conclude that a generalized staphylococcic infection can be cured by penicillin and that local lesions heal during its parenteral administration. The healing of bony lesions was particularly striking.

The most practical method of administration of the drug was by the intramuscular route at three hour intervals.

In assessing progress one should not focus attention too sharply on the temperature chart, since other features, such as diminution of pain and improvement in appetite and in sense of well-being, are often more important.

No toxic symptoms due to the drug were observed.

Local penicillin treatment was used for one hundred and seventy-two infections of the eye and the mastoid process, sinuses of chronic wounds and miscellaneous local septic conditions. In most cases after adequate treatment staphylococci and streptococci were eliminated, with subsequent healing.

LANGMANN, New York.

News and Comment

GENERAL NEWS

Physicians Certified by the American Board of Pediatrics.—The following physicians were certified as specialists by the American Board of Pediatrics after the examinations in San Francisco on May 6 and 7, 1944:

Robert Hamilton Alway, Salt Lake City, Utah; John Francis Belz, Portland, Ore.; Charles Henry Cutler, San Francisco (in the Army); Carl A. Erickson, Pasadena, Calif.; David M. Goldstein, San Luis Obispo, Calif. (in the Army); May B. Guy, Seattle; Paul Herzog, Kenosha, Wis. (in the Army); Arthur Henry Hurd, Pasadena, Calif.; Helen Marie Johnson, San Francisco; Evelynne Gwenneth Knouf, San Marino, Calif.; Donald C. Marshall, Honolulu, T. H.; Ann Lavinia Martin, Colorado Springs, Colo.; Mary B. Olney, San Francisco; Leonard Bolton Outlar, Wharton, Tex. (in the Navy); Agnes Groves Plate, San Francisco; Frederick W. Rutherford, Seattle; Milton C. F. Semoff, Albuquerque, N. Mex.; Spencer Snow, Salt Lake City, and William Herman Zavin, Portland, Ore.

Of 31 applicants examined at this meeting, 19 passed and 12 failed.

The American Board of Pediatrics, Inc.—The American Board of Pediatrics will hold a written examination on Friday, Sept. 22, 1944, locally under a monitor, for all candidates planning to take the oral examinations in the fall.

Oral examinations will be held in St. Louis on Nov. 8 and 9, 1944, and in New York on Dec. 15 and 16, 1944. Group I, the requirement for which is that an applicant shall have been specializing in pediatrics for ten years or more, will be abolished on July 1, 1944. All applicants regardless of qualifications must take both the written and the oral examination.

Directory of Medical Specialists.—The third edition of the Directory of Medical Specialists, listing names and biographic data of all men certified by the fifteen American boards, is to be published early in 1945. Collection of biographic data of the specialists certified since the 1942 edition was compiled and revision of the older listings in that volume are now going forward rapidly. Certified specialists are requested to make prompt return of notices regarding their biographies as soon as possible after receiving the proper forms.

CORRECTION

In the article by Dr. Herbert A. Wenner entitled "Complications of Infantile Eczema Caused by the Virus of Herpes Simplex," which appeared in the April issue (*Am. J. Dis. Child.* **67**:247, 1944), the following reference was omitted from page 264:

21. Goodpasture, E. W., and Teague, O.: Transmission of the Virus of Herpes Febrilis Along Nerves in Experimentally Infected Rabbits, J. M. Research **44**:139 (Dec.) 1923.

Book Reviews

Allergy. By Erich Urbach, M.D., and Philip M. Gottlieb, M.D. Price, $12.00. Pp. 1073, with 400 illustrations and 80 tables and charts. New York: Grune & Stratton, Inc., 1943.

This is an impressive book. Its authors are thinkers and have obviously thought a great deal about allergy. The book contains 1,013 pages of text, divided into three sections, as follows: "The Fundamentals of Allergy," 283 pages, "The Etiologic Agents of Allergic Diseases," 272 pages, and "The Symptomatology and Therapy of Allergic Diseases," 458 pages. There are 2,262 references. The paper and format are excellent. The illustrations are numerous, good and to the point.

It is not possible for any one to write a book on allergy with which every one would agree, particularly if the author proposes new classifications and nomenclatures. Such is the case with this book. In the first section, for example, a number of terms somewhat strange to American ears are used, such as "pathergy," "parallergy," "metallergy," "hypoergy" and positive and negative "anergy." "The concept of pathergy embraces all acquired and innate abnormally increased or decreased capacities of living tissues to react to the influence of chemical or physical agents, regardless of whether these agents be of the character of antigens or not." Pathergy includes allergic pathergy, heteroallergic pathergy and nonallergic pathergy, with several subdivisions, an arrangement which makes the classification somewhat complicated. The authors believe that Pirquet's definition of allergy is outmoded, and they will not admit that any condition is allergic unless it is medicated by antibodies. According to the ideas of authorities in America, this would separate most instances of contact dermatitis from the allergic group. The authors, however, believe that there is an antigen-antibody reaction in contact dermatitis, excluding dermatitis from primary irritants, whether it can be demonstrated or not, and so they speak of "allergic contact dermatitis." They reject Coca's conception of atopy but agree that heredity is one of the factors which may predispose to sensitization. In this section is included a discussion of the theoretic and practical aspects of desensitization, in which the authors highly recommend "propeptans," originated by one of them. They are also in favor of oral pollen and house dust therapy. These opinions are not shared by most allergists. This section of the book, whether or not one agrees with it, is well worth careful study, is exceedingly well written and consists in essence of a critical and philosophic review of a large number of contributions dealing with the fundamentals of allergy.

The second section, dealing with etiologic agents of allergic diseases, is most complete and well arranged and contains much valuable reference material. The extensive discussion of allergy in infectious diseases is particularly good.

The third section contains discussions of hay fever, asthma, dermatitis, urticaria and gastrointestinal allergy as well as of many other conditions not ordinarily allergic in origin. It is surprising to note, in view of the fact that the senior author is a dermatologist, that so little space is given to the local treatment of dermatitis, which in so many cases is more important than allergic investigation.

There is much that is good about this book; it is carefully written and is complete. It is obvious that the authors have a broad and a deep knowledge of allergy.

Its defects are that they discuss practically everything that any one has ever thought or written about allergy, whether or not it has been of permanent value; there are too many references to matters which are not accepted by most allergists. A great deal of the material that has appeared in the literature on allergy, particularly concerning treatment, is, to say the least, not sound. Some enthusiast thinks he has obtained good results in a few cases by some particular method of treatment and immediately writes a paper on it. His results cannot be duplicated by any other physician, and his methods are not generally accepted. Too much of such material is quoted and reviewed by the authors, and often highly recommended.

None the less, the reviewer is glad to own this book; he will profit by further study of it. So will any allergist who buys it. It is not recommended for general practitioners or for any one who is not a student of allergy.

Health and Physical Fitness. By Dr. I. H. Goldberger and Grace T. Hallock. Price, $1.92. Pp. 595, with 185 illustrations. Boston: Ginn and Co., 1943.

This text or reference book was written by Dr. I. H. Goldberger, assistant director of health education in the public schools of the city of New York, and Grace T. Hallock, director of the welfare publication bureau of the Metropolitan Life Insurance Company. It is primarily written to be used in high schools.

A style typical of textbooks is used, with comprehensive questions and a drill on vocabulary at the end of each chapter. The glossary at the end of the volume is fairly large and gives brief, simple definitions. Also, there is a good bibliography, divided into headings differentiating the various aspects of health, as a guide for further study. There are simple and adequate illustrations, both photographic and diagrammatic.

Intensive study of a book like "Health and Physical Fitness" should provide the high school student with a good introduction to the mental, physical, emotional and sociologic aspects of the healthful development of human beings.

This text brings the subject of health up to date by including such topics as the development of the use of the sulfonamide drugs in therapeutics, the preparation and use of dried blood plasma, industrial hygiene, the Kenney treatment for poliomyelitis, the standards for acceptance into the armed forces, civilian defense and, in the section on budgeting, the need for buying war bonds. Also in the section on budgeting, there is a discussion of the difficulties encountered in planning to include medical care unless it is provided for by insurance or by socialization of medicine.

The broad contents of the book are divided into four sections. Part I, "Your Equipment for Living and How to Use It," covers one's physical equipment at birth, anatomy, physical culture, nutrition and allied subjects. Part II, "Your Personality and How to Enrich It," includes a description of the nervous system and its diseases and discussions of personality,

heredity and personality changes. This section is concerned with the effects of narcotics, alcohol, smoking and self medication. Part III, "Your Home and Community and How to Make Them Healthful," and part IV, "Your Future and How to Face It," are primarily concerned with the sociologic aspects of health, plus a section on first aid and accident control.

Although this book gives as "facts" some highly controversial opinions, it is in general a good textbook for high school students.

Rheumatic Fever in Children, Its Recognition and Management. Written and edited by a group of distinguished clinicians and organizations. Price, available to physicians without charge. Pp. 32, with 3 illustrations. New York: Metropolitan Life Insurance Company, 1943.

A 32 page booklet is now available to physicians, without charge, entitled "Rheumatic Fever in Children, Its Recognition and Management." It has been written and edited by a group of distinguished clinicians and organizations and is published by the Metropolitan Insurance Company, in New York.

It is rare to encounter such a condensed, accurate and authoritative work. For all who wish to review their knowledge of rheumatic fever or get an excellent summary of the latest information about the disease, the possession of a copy will be worth while.

Not only has the booklet a full account of the nature, diagnosis, course, prognosis and care of the disease, laboratory aids for its recognition and public health considerations of rheumatic fever, but it has suggestions for further reading and a number of helpful appendixes. A map in the booklet surprised the reviewer by showing that the death rate per hundred thousand is higher in Idaho, Montana, Colorado and Utah than it is in Illinois, Wisconsin or Michigan. The pictures of certain of the clinical manifestations are excellent.

An italicized summary of what to do when rheumatic fever is active and when it is inactive gives the booklet a practical quality. One should be sure to put somewhere in one's consciousness these lines concerning the treatment of the child with inactive rheumatic fever: "Encourage physical activity to the limit of the child's capacity. Only a small percentage of children at adolescence are found to have sufficient permanent heart disease to preclude normal activity. Discourage parents and teachers from making a chronic invalid of the child. Educational authorities need to know that the vast majority who attend regular schools when the disease is inactive can and should engage in normal school life."

Convulsive Seizures. By Tracy Putnam, M.D. Price, $2.00. Pp. 168, with 12 illustrations. Philadelphia: J. B. Lippincott Company, 1943.

This is "A Manual for Patients, their Families and Friends." Written by an outstanding authority, the book gives a scientific description of the personal, medical and social aspects of the condition for the laity; the causes, symptoms, diagnosis, treatment and prognosis of epilepsy, or convulsive disorders, are simply and interestingly described. The social restrictions, as automobile driving, employment, marriage and progeny, are discussed from a medical point of view throughout the book. The final chapter is devoted to the legal problems presented by persons with this type of disorder.

The book is written in an extremely interesting style. It presents a scientific and practical attitude, which should be of great value to these patients and their families.

Directory of Pediatric Societies *

INTERNATIONAL

International Association of Preventive Pediatrics

President: Prof. S. Monrad, Dronning Louises Børnehospital, Copenhagen, Denmark.
Secretary: Dr. Daniel Oltramare, 15 Rue Lévrier, Geneva, Switzerland.

International Congress of Pediatrics

President: Dr. Henry F. Helmholz, Mayo Clinic, Rochester, Minn.
Secretary-Treasurer: Dr. Charles F. McKhann, University Hospital, Ann Arbor, Mich.
Canadian Committee:
Chairman: Dr. Alan Brown, Hospital for Sick Children, 67 College St., Toronto.
Secretary: Dr. H. P. Wright, 1509 Sherbrooke St. W., Montreal.
Place: Boston. Time: Postponed indefinitely.

International Congress for the Protection of Infancy

Secretary: Prof. G. B. Allaria, Corso Bramante 29, Torino 120, Italy.

FOREIGN

Argentine Pediatric Society of Buenos Aires

President: Dr. Martin Ramón Arana, 1809 Rodriguez Peña, Buenos Aires.
General Secretary: Dr. Alfredo Larguia, Cerrito 1179, Buenos Aires.

Associação Paulista de Medicina, Section on Pediatrics

President: Dr. Vicente Lara.
First Secretary: Dr. Armando de Arruda Sampaio.
Second Secretary: Dr. Paulo de Barros Franca, Av. Brigadeiro Luiz Antonio 393, 1° Andar, São Paulo, Brazil.

British Paediatric Association

President: Prof. L. G. Parsons, 58 Calthorpe Rd., Five Ways, Birmingham.
Secretary: Dr. Donald Paterson, 27 Devonshire Pl., London, W. 1.

Danish Pediatric Society

President: Dr. E. Lenstrup, Copenhagen.
Secretary: Dr. E. Gjørup, Dronning Louises Børnehospital, Copenhagen.

Nederlandische Vereeniging voor Kindergeneeskunde

President: Dr. J. H. G. Carstens, Servaasbolwerk 14ª, Utrecht.
Secretary: Dr. R. P. van de Kasteele, Laan van Poot 340, 's Gravenhage.
Place: Different places. Time: Three times a year.

Paediatrický Spolok na Slovensku

President: Dr. A. J. C. Chura, Lazaretská 11, Bratislava.
Secretary: Dr. P. Rados, Lazaretská 6, Bratislava.
Place: Pediatric Clinic, University Bratislava. Time: Six times a year.

Royal Society of Medicine, Section for the Study of Disease in Children

President: Dr. E. A. Cockayne, 98 Harley St., London, W. 1, England.
Secretary: Dr. R. Lightwood, 86 Brook St., London, W. 1, England.
Place: 1 Wimpole St., London. Time: Fourth Friday of each month, 4:15 p. m.

Palestine Jewish Medical Association, Section of Physicians of Children's Diseases

President: Prof. S. Rosenbaum, 26 Bialkstr., Tel Aviv.
Secretary: Dr. A. Brünn, 9 Maazestre, Tel Aviv.

Sociedad Cubana de Pediatria

President: Dr. Angel A. Aballí Arellano, 17 No. 609 Vedado, Habana.
Secretary: Dr. Julio G. Cabrera Calderin, Hospital Mercedes L y 21 (Vedado), Box 2430, Habana.
Place: Cátedra de Clinica Infantil, Hospital Mercedes, Habana. Time: Last Wednesday of every month.

Sociedad Mexicana de Pediatria

President: Dr. Fernando López Clares, 12/a. Medellín 191, Mexico.
Secretary: Dr. Jesus Gómez Pagola, Versalles 64, Mexico.

Sociedad Venezolana de Puericultura y Pediatria

President: Dr. E. Santos Mendoza.
Secretary: Dr. P. Oropeza, Hospital de Niños, Caracas.

Société de Pédiatrie de Paris

President: Dr. B. Weill-Hallé, 49 Avenue Raymond Poincare, Paris, France.
Secretary: Dr. Jean Hallé, 10 bis Rue Pré aux Clercs, Paris, France.
Place: Hôpital des Enfants Malades, 49 Rue de Sèvres. Time: 4:30 p. m., third Thursday of every month.

Uruguyan Society of Pediatrics

President: Dr. Jose Alberto Praderi, Eduardo Acevedo 1132, Montevideo.
Secretary: Dr. Alfredo Ramon Guerra, Paysandú 824, Montevideo.

NATIONAL

American Medical Association, Scientific Assembly, Section on Pediatrics

Chairman: Dr. John Aikman, 184 Alexander St., Rochester, N. Y.
Secretary: Dr. Gilbert J. Levy, 188 S. Bellevue Blvd., Memphis, Tenn.

American Academy of Pediatrics

President: Dr. Franklin P. Gengenbach, 1850 Gilpin St., Denver, Colo.
Secretary: Dr. Clifford G. Grulee, 636 Church St., Evanston, Ill

* Secretaries of societies are requested to furnish the information necessary to make this list complete and to keep it up to date.

American Hospital Association, Children's Hospital Section

Chairman: Dr. Joelle C. Hiebert, 299 Main St., Lewiston, Maine.
Secretary: Dr. W. Franklin Wood, McLean Hospital, Waverly, Mass.

American Pediatric Society

President: Dr. James L. Gamble, 300 Longwood Ave., Boston.
Secretary-Treasurer: Dr. Hugh McCulloch, 325 N. Euclid Ave., St. Louis.

Canadian Society for the Study of Diseases of Children

President: Dr. R. R. Struthers, 906 Drummond Medical Bldg., Montreal.
Secretary-Treasurer: Dr. Elizabeth Chant Robertson, Hospital for Sick Children, Toronto.

Society for Pediatric Research

President: Dr. Joseph A. Johnston, Henry Ford Hospital, Detroit.
Secretary: Dr. Mitchell I. Rubin, 1740 Bainbridge St., Philadelphia.

SECTIONAL

Intermountain Pediatric Society

President: Dr. Eugene Smith, 385-24th St., Ogden, Utah.
Secretary-Treasurer: Dr. W. C. Cheney, 837 Boston Bldg., Salt Lake City.
Place: Salt Lake City General Hospital. Time: First Thursday of each month, 8 p. m.

New England Pediatric Society

President: Dr. Warren R. Sisson, 319 Longwood Ave., Boston.
Secretary-Treasurer: Dr. James Marvin Baty, 1101 Beacon St., Brookline, Mass.
Place: Boston Medical Library. Time: Four meetings a year, occurring from September to May.

North Pacific Pediatric Society

President: Dr. M. L. Bridgeman, 1020 S. W. Taylor St., Portland, Ore.
Secretary: Dr. C. G. Ashley, 833 S. W. 11th Ave., Portland, Ore.

Northwestern Pediatric Society

President: Dr. Arild E. Hansen, University of Minnesota, Minneapolis.
Secretary-Treasurer: Dr. Albert V. Stoesser, 205 W. University Hospital, Minneapolis.
Place: Minneapolis, St. Paul, Duluth and Rochester. Time: January, April, July and October.

Rocky Mountain Pediatric Society

President: Dr. G. R. Fisher, 23 E. Pikes Peak Ave., Colorado Springs, Colo.
Secretary: Dr. Joseph H. Lyday, 1850 Gilpin St., Denver.

Southern Medical Association, Section of Pediatrics

Chairman: Dr. William Weston Jr., 1428 Lady St., Columbia, S. C.
Secretary. Dr. Angus McBryde, 604 W. Chapel Hill St., Durham, N. C.

STATE

Alabama Pediatric Society

President: Dr. Amas Gipson, 948 Forrest Ave., Gadsen.
Secretary-Treasurer: Dr. Ruth Berrey, 2021-6th Ave. N., Birmingham.

Arizona Pediatric Society

President: Dr. Vivian Tappan, San Clemente, Tucson.
Secretary: Dr. Hilda Kroeger, Arizona State Health Dept. (Maternal and Child Welfare Division), Phoenix.

Arkansas State Pediatric Association

Chairman: Dr. C. B. Billingsley, 1425 N. 11th St., Fort Smith.
Secretary: Dr. R. E. Weddington, 1425 N. 11th St., Fort Smith.

California State Medical Society, Section on Pediatrics

Chairman: Dr. William C. Deamer, University of California Hospital, San Francisco.
Secretary: Dr. Charles W. Leach, 2000 Van Ness Ave., San Francisco.

Florida State Pediatric Society

President: Dr. Ludo Von Meysenbug, Box 3356, Daytona Beach.
Secretary: Dr. Robert Blessing, 409 Blount Bldg., Ft. Lauderdale.
Place: Concurrent with state association meeting at time of convention.

Georgia Pediatric Society

President: Dr. T. F. Davenport, 104 Ponce de Leon Ave. N. E., Atlanta.
Secretary-Treasurer: Dr. Don F. Cathcart, 478 Peachtree St. N. E., Atlanta.

Hezekiah Beardsley Pediatric Club of Connecticut

President: Dr. Edward T. Wakeman, 129 Whitney Ave., New Haven.
Secretary: Dr. Herman Yannet, Southbury Training School, Southbury.
Time: Three meetings a year.

Illinois State Medical Society, Section on Pediatrics

Chairman: Dr. Craig D. Butler, 715 Lake St., Oak Park.
Secretary: Dr. A. J. Fletcher, 139 N. Vermilion, Danville.

Indiana State Pediatric Society

President: Dr. K. T. Knode, 1105 E. Jefferson Bldg., South Bend.
Secretary-Treasurer: Dr. Mathew Winters, 621 Hume Mansur Bldg., Indianapolis.
Time: Two meetings a year.

Iowa Pediatric Society

President: Dr. Mark L. Floyd, Children's Hospital, Iowa City.
Secretary-Treasurer: Dr. James Dunn, Davenport Bank Bldg., Davenport.

MEDICAL SOCIETY OF STATE OF NEW YORK, SECTION ON PEDIATRICS

Chairman: Dr. A. Clement Silverman, 608 E. Genesee St., Syracuse.
Secretary: Dr. Albert G. Davis, 307 Gas and Electric Bldg., Utica.

MEDICAL SOCIETY OF THE STATE OF PENNSYLVANIA, PEDIATRIC SECTION

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Secretary: Dr. P. F. Lucchesi, Philadelphia Hospital, Philadelphia.

MICHIGAN STATE MEDICAL SOCIETY, PEDIATRIC SECTION

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NEBRASKA PEDIATRIC SOCIETY

President: Dr. E. W. Hancock, 820 Sharp Bldg., Lincoln.
Secretary-Treasurer: Dr. John M. Thomas, 1102 Medical Arts Bldg., Omaha.
Place: As announced by committee. Time: Third Thursday of each month from October to June, inclusive. Dinner at 6 p. m.

NEW HAMPSHIRE PEDIATRIC SOCIETY

President: Dr. MacLean J. Gill, 14 N. State St., Concord.
Secretary-Treasurer: Dr. Ursula G. Sanders, 46 Pleasant St., Concord.
Time: Twice yearly.

NORTH CAROLINA PEDIATRIC SOCIETY

President: Dr. Arthur H. London, 1105 W. Main St., Durham.
Secretary: Dr. Jay M. Arena, 604 W. Chapel Hill St., Durham.

OKLAHOMA STATE PEDIATRIC SOCIETY

President: Dr. Ben H. Nicholson, 301 N. W. 12th St., Oklahoma City.
Secretary: Dr. Luvern Hays, 108 W. 6th St., Tulsa.
Place: Oklahoma Club. Time: 6:30 p. m., fourth Friday of each alternate month from September to May, inclusive.

SOUTH CAROLINA PEDIATRIC SOCIETY

President: Dr. Lonita Boggs, 301 E. Coffee St., Greenville.
Secretary-Treasurer: Dr. Hilla Sheriff, Wade Hampton Office Bldg., Columbia.

TEXAS PEDIATRIC SOCIETY

President: Dr. F. H. Lancaster, 4409 Fannin St., Houston.
Secretary-Treasurer: Dr. John E. Ashby, 3610 Fairmount Ave., Dallas.

VIRGINIA PEDIATRIC SOCIETY

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Secretary: Dr. Emily Gardner, 1100 W. Franklin St., Richmond.

WEST VIRGINIA STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

President: Dr. Andrew Amick, 1021 Quarrier St., Charleston.
Secretary: Dr. A. A. Shawkey, Professional Bldg., Charleston.

LOCAL

ACADEMY OF MEDICINE OF CLEVELAND PEDIATRIC SECTION

Chairman: Dr. J. D. Nourse, 10515 Carnegie Ave., Cleveland.
Secretary: Dr. I. B. Silber, 10465 Carnegie Ave., Cleveland.
Place: Cleveland Medical Library Bldg. Time: October, December, February and April.

ACADEMY OF MEDICINE, TORONTO, SECTION OF PEDIATRICS

President: Dr. I. Nelles Silverthorne, 170 St. George St., Toronto, Canada.
Secretary: Dr. G. P. Hamblin, 2333 Bloor St. W., Toronto, Canada.

BRONX PEDIATRIC SOCIETY

President: Dr. Harry J. Cohen, 1975 Walton Ave., New York.
Secretary: Dr. Walter Levy, 12 E. 88th St., New York.
Place: Concourse Plaza Hotel, 161st St., and Grand Concourse. Time: Second Wednesday of each month, except June, July, August and September.

BROOKLYN ACADEMY OF PEDIATRICS

President: Dr. Harry A. Naumer, 37–8th Ave., Brooklyn.
Secretary: Dr. Lewis A. Koch, 62 Pierrepont St., Brooklyn.
Place: Granada Hotel. Time: Fourth Wednesday of October, November, February, March and April.

BUFFALO PEDIATRIC SOCIETY

President: Dr. A. Wilmot Jacobsen, 187 Bryant St., Buffalo N. Y.
Secretary: Dr. Richard A. Downey, 786 Forest Ave., Buffalo, N. Y.
Place: Children's Hospital, 219 Bryant St. Time: 8:30 p. m., first Monday of each month from September to June.

CENTRAL NEW YORK PEDIATRIC CLUB

President: Dr. Edward J. Wynkoop, 501 James St., Syracuse.
Secretary: Dr. Frank J. Williams, 58 S. Swan St., Albany.
Places:: Various cities in New York. Time: Third Tuesday of April and September.

CHICAGO PEDIATRIC SOCIETY

President: Dr. Heyworth N. Sanford, 952 N. Michigan Ave., Chicago.
Secretary: Dr. Henry G. Poncher, 1819 W. Polk St., Chicago.
Place: Children's Memorial Hospital, 710 Fullerton Ave. Time: Third Tuesday of each month, October to May, Inclusive.

Cincinnati Pediatric Society

President: Dr. Lloyd K. Felter, 3144 Jefferson Ave., Cincinnati.
Secretary: Dr. T. Selkirk, 3530 Reading Rd., Cincinnati.
Place: Children's Hospital, Elland Ave., Cincinnati. Time: On call.

Dallas Pediatric Society

President: Dr. John E. Ashby, 3610 Fairmount Ave., Dallas, Texas.
Secretary-Treasurer: Dr. Gladys J. Fashena, 4585 Belfort, Dallas, Texas.
Place: Bradford Baby Hospital. Time: 1 p. m., second and fourth Saturdays of each month.

Detroit Pediatric Society

President: Dr. Hugh Lewis, Detroit, Mich.
Secretary: Dr. John J. Pollack, 622-26 Maccabees Bldg., Detroit, Mich.
Place: Wayne County Medical Society. Time: 8:30 p. m., first Wednesday of each month from October to June, inclusive.

Fulton County Medical Society, Pediatrics Section (Atlanta, Ga.)

Chairman: Dr. Don F. Cathcart, 478 Peachtree St. N. E., Atlanta.
Secretary: Dr. Harry Lange, 478 Peachtree St., N. E., Atlanta.
Place: Academy of Medicine, 38 Prescott St. N. E. Time: Second Thursday of each month from October to April, 8 p. m.

Houston Pediatric Society

President: Dr. Raymond Cohen, 2300 Caroline St., Houston, Texas.
Secretary: Dr. Betty Moody, 526 Richmond Rd., Houston, Texas.
Place: College Inn, Houston. Time: Fourth Monday of each month.

Kansas City (Missouri) Pediatric Society

President: Dr. Edwin H. Schorer, 1103 Grand Ave., Kansas City.
Secretary: Dr. H. E. Petersen, Kirkpatrick Bldg., St. Joseph, Mo.
Place: Kansas City General Hospital. Time: On call.

Los Angeles County Medical Association, Pediatric Section

President: Dr. Oscar Reiss, 2200 W. 3d St., Los Angeles.
Secretary-Treasurer: Dr. Elena Boder, 1830½ Lucille Ave., Los Angeles.
Place: Los Angeles County Medical Headquarters, 1925 Wilshire Blvd. Time: Second Monday of February, April, June, October and December.

Medical Society of the County of Kings and the Academy of Medicine of Brooklyn, Pediatric Section

President: Dr. Harry Bikoff, 850 St. Marks Ave., Brooklyn.
Secretary: Dr. Henry Rascoff, 895 Eastern Parkway, Brooklyn.
Place: 1313 Bedford Ave., Brooklyn. Time: 9:00 p. m., fourth Monday of each month, October to April, inclusive.

Medical Society of the County of Queens, Inc., Section on Pediatrics

Chairman: Dr. Meyeron Coe, 217-02-91st Ave., Queens Village, N. Y.
Secretary-Treasurer: Dr. Edith A. Mittell, 144-38th Ave., Flushing, N. Y.
Place: Queens County Medical Bldg., Forest Hills, N. Y. Time: Third Monday of October, January, March and May.

Medical Society of the District of Columbia, Section on Pediatrics

President: Dr. Harry A. Spigel, 2647 Connecticut Ave., Washington, D. C.
Secretary-Treasurer: Dr. Perry W. Gard, 2520 Woodley Rd., Washington, D. C.
Place: Medical Society Bldg., 1718 M St. N. W. Time: 8 p. m., fourth Thursday of every month.

Memphis Pediatric Society

President: Dr. F. T. Mitchell, 376 S. Bellevue Ave., Memphis, Tenn.
Secretary-Treasurer: Dr. Harry Jacobson, 1193 Madison Ave., Memphis, Tenn.
Place: John Gaston Hospital. Time: Quarterly.

Milwaukee Pediatric Society

President: Dr. John H. Reynolds, 1628 W. Wisconsin Ave., Milwaukee.
Secretary-Treasurer: Dr. F. J. Mellencamp, 324 E. Wisconsin Ave., Milwaukee.
Place: Milwaukee Athletic Club. Time: Second Wednesday of each alternate month, beginning with February.

New York Academy of Medicine, Section of Pediatrics

Chairman: Dr. Howard Craig, 175 E. 79th St., New York.
Secretary: Dr. Alfred E. Fischer, 73 E. 90th St., New York.
Place: New York Academy of Medicine, 2 E. 103d St. Time: Second Thursday of each month from October to May, inclusive, 8:30 p. m.

Northern California Affiliates

President: Dr. Crawford Bost, 490 Post St., San Francisco.
Secretary: Dr. William A. Reilly, 384 Post St., San Francisco.
Time: Second Thursday of September, November, January, March and May.

Oklahoma City Pediatric Society

President: Dr. William M. Taylor, 1200 N. Walker St., Oklahoma City.
Secretary: Dr. G. R. Felts, 625 N. W. 10th St., Oklahoma City.
Place: Oklahoma Club. Time: Third Thursday of each month.

Philadelphia Pediatric Society

President: Dr. Theodore S. Wilder, Greene and Coulter Sts., Germantown, Philadelphia.
Secretary: Dr. Sherman Little, 1740 Bainbridge St., Philadelphia.
Place: College of Physicians, 19 S. 22d St. Time: Second Tuesday in March, May, October and December.

Pittsburgh Pediatric Society

President: Dr. Carl Ruder, 646 Washington Rd., Mount Lebanon, Pittsburgh.

Secretary-Treasurer: Dr. C. J. Stoecklein, 125 De Soto St., Pittsburgh.

Place: Pittsburgh Academy of Medicine. Time: Second Friday, alternate month from October to June, inclusive.

Richmond Pediatric Society

President: Dr. Stanley Meade, 913 Floyd Ave., Richmond, Va.

Secretary-Treasurer: Dr. Louise Galvin, 214 S. Boulevard, Richmond, Va.

Place: Richmond Academy of Medicine, 1200 E. Clay St. Time: 8 p. m., third Thursday of each month, except June, July and August.

Rochester Pediatric Society

President: Dr. Herbert Soule, 122 Rutgers St., Rochester, N. Y.

Secretary-Treasurer: Dr. Jerome Glaser, 300 S. Goodman St., Rochester, N. Y.

Place: Rochester Academy of Medicine or arrangement by program committee. Time: Third Friday of each month from October to May.

St. Louis Pediatric Society

President: Dr. Jerome Diamond, 508 N. Grand Ave., St. Louis.

Secretary-Treasurer: Dr. Mary A. McLoon, 408 Humboldt Bldg., St. Louis.

Place: St. Louis Medical Society Bldg. Time: First Friday of each month from November to June.

Seattle Pediatric Society

President: Dr. Frederick B. Joy, Stimson Bldg., Seattle.

Secretary: Dr. Sherod M. Billington, Medical Dental Bldg., Seattle.

Place: College Club. Time: Third Friday of each month from September to June at 6:30 p. m.

Southwestern Pediatric Society

President: Dr. Jeanette Harrison, 1136 W. 6th St., Los Angeles.

Secretary: Dr. Henry F. Gallagher, 1930 Wilshire Blvd., Los Angeles.

Place: Jonathan Club of Los Angeles. Time: First Wednesday in January, March, May, September and November.

University of Michigan Pediatric and Infectious Disease Society

President: Dr. Campbell Harvey, 35 W. Huron St., Pontiac, Mich.

Secretary: Dr. Harry A. Towsley, University of Michigan, Department of Pediatrics and Communicable Diseases, Ann Arbor, Mich.

Westchester County Medical Society, Pediatrics Section (New York)

President: Dr. John B. Ahouse, 27 Ludlow St., Yonkers, N. Y.

Secretary-Treasurer: Dr. Elvira Ostlund, 64 Highland Rd., Rye, N. Y.

Place: Grasslands Hospital, Valhalla, N. Y. Time: Third Thursday in October, December, February and April.

INDEX TO VOLUME 67

The asterisk (*) preceding the page number indicates an original article. Subject entries are made for all articles. Author entries are made for original articles and society transactions. Book Reviews, Obituaries and Society Transactions are indexed under the letters B, O and S, respectively.

Abdomen: See Gastrointestinal Tract; Pelvis
Abnormalities and Deformities: See Cripples; Monsters; Twins; and under names of diseases, organs and regions, as Aortic Valve; Brain; Cerebellum; Eyes; Genitourinary Tract; Heart; Intestines; Skin; etc.
Abscess: See also under names of organs and regions, as Brain, abscess; Lungs, abscess; etc.
parapharyngeal, in children, 495
Accommodation: See Eyes, accommodation and refraction
Acetylcholine: See Choline and Choline Derivatives
Achalasia: See Sphincter Muscles
Achlorhydria: See under Stomach
Acid, Amino: See Amino Acids
Ascorbic: See Ascorbic Acid
Cevitamic: See Ascorbic Acid
effectiveness of linoleic, arachidonic and linolenic acids in reproduction and lactation, 58
Fatty: See Blood, fatty acids
Nicotinic: See Nicotinic Acid
Pantothenic: See Vitamins, B
sulfanilamide bacteriolysis in presence of mercuric chloride and *p*-aminobenzoic acid, 501
Tannic: See Burns; Tannin
Acid-Base Equilibrium: See also Acidosis; etc.
effect of continued sulfanilamide ingestion on acid-base equilibrium of dog, 501
physicochemical respiratory regulation and acid-base equilibrium in children, 79
Acidosis: See also Acid-Base Equilibrium
ketosis in relation to hepatic reserves of glycogen: study of normal and of diabetic children, *100
Acrodynia, body fats in rat acrodynia, 84
Acrolein and shock; possible relationship of lipoid breakdown products to shock associated with burns, 499
Acromioclavicular Joint: See Shoulder
Actinomycosis, 70
Adenitis: See Lymph Nodes
Adipose Tissue: See Fat; Obesity
Adiposogenital Syndrome: See Laurence-Moon-Biedl Syndrome
Adolescence, blood pressure of adolescents, 494
Delinquency in: See Delinquency
Precocious: See Puberty
prognostic factors of adolescent psychoses, 81
tuberculosis in adolescents and young adults, 233
Adrenal Preparations, antagonism of pitressin and adrenal cortical extract in human diabetes insipidus, 83
effect on electrical activity of cortex of certain depressant and stimulant drugs; barbiturates, morphine, caffeine, benzedrine and adrenalin, 497
pharmacologic study of epinephrine suspensions in oil, 240
role of anterior pituitary in adrenalin hyperglycemia and liver glycogenolysis, 82
Adrenalectomy: See under Adrenals
Adrenalin: See Adrenal Preparations
Adrenals, adrenal cortical hyperplasia with virilism; diagnosis, course and treatment, 83
adrenocortical-like tissue in ovaries of adrenalectomized ground squirrel (Citellus tridecemlineatus), 419
effect of adrenal factors on plasma proteins, 82
effect of diet in rats on adrenal weights and on survival following adrenalectomy, 418
effect of high protein diets on size and activity of adrenal cortex in albino rat, 418
hemorrhage, bilateral, 419
Adrenals—Continued
hemorrhage; purpura fulminans (Waterhouse-Friderichsen syndrome); report of case with recovery, 329
review of adrenal cortical hypertrophy, 418
Age, attack rate and incubation period of measles; significance of age and of conditions of exposure, *15
experimental studies with dermatophytes; influence of age on allergic response in experimental ringworm in guinea pig, 239
Agglutinins and Agglutination: See also Blood, groups; Immunity; Whooping Cough; etc.
presence of Rh antibodies in breast milk; further investigations, 401
Agglutinogen: See Whooping Cough
Agnosia: See Vision, defective
Ailanthus: See Hay Fever
Air, bactericidal action of ultraviolet radiation on air-borne organisms, 56
initial aerobic flora of newborn (premature) infants; nature, source and relation to ultraviolet irradiation and face masks, *89
studies on air-borne infection in hospital ward; effect of ultraviolet light on cross-infection in infants' ward, 66
studies on air-borne infection in hospital ward; effects of ultraviolet irradiation and propylene glycol vaporization on prevention of experimental and air-borne infection of mice by droplet nuclei, 66
studies on air-borne virus infections, 321
Air Passages: See Respiratory Tract
Albumin: See under Blood, proteins; Proteins
Alimentary Canal: See Intestines
Intoxication: See Digestive System
Tract: See Digestive System
Allergens: See Anaphylaxis and Allergy
Allergy: See Anaphylaxis and Allergy; Asthma; Food, allergy; Hay Fever; etc.
Alloxan, necrosis of islets of Langerhans produced experimentally (by styrl quinoline and alloxan), 415
Altitude: See Aviation and Aviators
Amaurosis: See Blindness
Amblyopia: See Blindness
Amebiasis; dysenteries, 319
Amentia: See Idiocy
Amino Acids: See also Nitrogen; Proteins
plasma amino acid retention, as evidence of impaired liver function; investigations in children with nephrosis and liver disease, 400
Aminophyllin: See under Blood
Ammonia and Ammonium Compounds, observations on C T A B (cetavlon); its use in surgery, 500
Amphetamine, effect on electrical activity of cortex of certain depressant and stimulant drugs; barbiturates, morphine, caffeine, benzedrine and adrenalin, 497
Amylase: See under Blood
Amyotonia: See Myatonia
Anaphylaxis and Allergy: See also Asthma; Food, allergy; Hay Fever; etc.
absorption of allergens, 84
allergy in identical twins, report on 7 pairs of twins, 84
antibodies to histamine induced in human beings by histamine conjugates, 420
deficiency anemia in infants; report of 2 cases, with associated temporary deficiency of anti-anemic factor in 1 and allergy and abnormal digestion of protein in other, *341
disappearance of tuberculin reaction in children under treatment for allergies, 322
experimental studies with dermatophytes; influence of age on allergic response in experimental ringworm in guinea pig, 239
histaminase in treatment of allergy in children, 421

Anaphylaxis and Allergy—Continued
immunity to tetanus induced by third dose of toxoid 3 years after basic immunization, based on study of 38 allergic children, *22
principles of diagnosis and treatment of allergy as related to otolaryngology, 422
relationship of eosinophil response to factors involved in anaphylaxis, 239
resistance to diseases in childhood, 502
Anderson, N. A.: Oral moniliasis in newborn infants, *450
Anderson, R. G.: Development and growth of human embryo and fetus; graphic representation of some aspects, *167
Anemia, aplastic; panmyelophthisis in child, 234
Cooley's: See Anemia, erythroblastic
deficiency, in infants; report of 2 cases, with associated temporary deficiency of antianemic factor in 1 and allergy and abnormal digestion of protein in other, *341
erythroblastic, of Cooley (familial erythroblastic anemia) in Indian boy, *290
hemolytic, chronic, with paroxysmal nocturnal hemoglobinuria (Marchiafava-Micheli syndrome); report of case with marked thrombocytopenia in 5 year old child, 324
hemolytic, congenital, in nursing infant, 149
hemolytic; hemolysins in acute hemolytic anemia, 411
hypochromic; achlorhydric hypochromic microcytic anemia in child of 8 years, 234
hypochromic, in infancy, 149
hypochromic, with koilonychia (spoon nails), 149
in women and children on wartime diets, 234
influence of diet on physiologic anemia of infants, 71
Mediterranean: See Anemia, erythroblastic
nutritional, in children and women; wartime problem, 325
refractory, studies in, 412
tolerance of frequent and repeated blood transfusions in children with anemias, 149
Anencephaly: See Monsters, cephalic
Anesthesia, fatalities and constitutional reactions following use of pontocaine [tetracaine hydrochloride], 330
Aneurysm, congenital aneurysmal dilatation of aorta associated with arachnodactyly, 403
congenital subaortic stenosis, with deformity of aortic valve, 494
intracranial, 416
Angina: See Throat; Tonsils
Angioid Streaks: See Retina, blood supply
Angioma, angiomatosis retinae (von Hippel-Lindau disease); report on genealogic tree, 158
Anhydrase: See Blood, enzymes
Ankylosis: See Joints
Anodontia: See Teeth
Anomalies: See under names of organs and regions
Anoxia: See Oxygen, deficiency
Anthropometry: See Adolescence; Children; Growth; etc.
Antigens and Antibodies: See Agglutinins and Agglutination; Immunity; and under specific antigens and reactions, as Keratoconjunctivitis; Staphylococci; Whooping Cough; etc.
Antithrombin: See Blood, coagulation
Antitoxin: See under Diphtheria; Scarlet Fever; Staphylococci; Tetanus; Whooping Cough
Anuria: See Urine, suppression
Aorta, congenital aneurysmal dilatation of aorta associated with arachnodactyly, 403
Aortic Valve, congenital subaortic stenosis, with deformity of, 494
Aphasia; epitome of agnosia, apraxia and aphasia with proposed physiologic-anatomic nomenclature, 154
Aphthae: See Stomatitis
Apnea Neonatorum: See Asphyxia
Apparatus, bactericidal action of ultraviolet radiation on air-borne organisms, 56
dactyloscopy in identification of newborn infants, 229
improved method for determining sedimentation rate of red blood corpuscles, 324
treatment of femoral shaft fractures in infants, 159
Appelbaum, E.: Pneumococcic meningitis; complete recovery of 6 month old infant treated with penicillin, *485
Apraxia; epitome of agnosia, apraxia and aphasia with proposed physiologic-anatomic nomenclature, 154
Arachnodactylia, congenital aneurysmal dilatation of aorta associated with arachnodactyly, 403
in 4 siblings with pneumoencephalographic observations of 2, *201
Marfan's syndrome, 144
Arachnoid, inflammation; optochiasmic arachnoiditis, 415
Armies: See Aviation and Aviators; Military Medicine
Arms, hemangioma of arm causing delay in delivery and neonatal death, 404
Arsenic and Arsenic Compounds: See also Tryparsamide
comparative effectiveness of arsenical compounds and sulfonamide drugs against bacterial infections, 408
liver extract in arsenical intolerance, 240
Therapy: See under Syphilis
Arteries: See Aneurysm; Aorta; Blood, pressure; Endarteritis; Thrombosis; etc.
Arthritis, meningococcosis of locomotor apparatus, 319
Still's (multiple rheumatoid arthritis) disease, 157
Arthrogryposis Multiplex Congenita: See Joints, ankylosis; Muscles, abnormalities
Ascaris, experimental eosinophilia with keratin from Ascaris suum and other sources, 65
lumbricoides; intussusception, 152
Ascorbic acid and complement; study of their relationship, 315
availability for human nutrition of vitamin C in raw cabbage and home-canned tomato juice, 402
estimation of "true" ascorbic acid in urine, 489
influence of variety, size and degree of ripeness on ascorbic acid content of peaches, 489
relation of season, weight and price to vitamin C content of oranges, 489
riboflavin and thiamine content of cow's milk; influence of ration, *376
vitamin C saturation test, 402
Ash, R.: Electrocardiographic variations in acute glomerulonephritis, *106
Aspergillus, flavicin; antibacterial substance produced by Aspergillus flavus, 487
Asphyxia: See also Respiration
fetal distress during labor, 403
neonatorum, 87
of newborn and its treatment, 144
respiratory disturbances in newly born infant, 463
treatment in newborn by administration of carbon dioxide to mother, 317
Asthma: See also Anaphylaxis and Allergy
allergy in childhood, 239
bronchial, blood pressure fluctuations in, 496
bronchial, therapeutic procedures in, 235
comparison of sodium and potassium metabolism of asthmatic and nonallergic children, 421
in childhood, 413
intractable, repeated bronchial relaxation in treatment of, 421
Atelectasis: See Lungs, collapse
Atmosphere: See Air
Atopy: See Anaphylaxis and Allergy
Atrophy: See under names of organs and regions, as Cerebellum; etc.
Infantile: See Celiac Disease
Muscular: See Dystrophy, muscular
Aviation and Aviators, airplane altitude flights in whooping cough, 147
Avitaminosis: See under Vitamins; and under names of deficiency diseases

B C G: See Tuberculosis
Bacilli: See Bacteria
Backache, congenital narrowing of lumbosacral space, 497
Backward Children: See Nervous and Mental Disabilities
Bacteria: See also Diphtheria; Meningococci; Pneumococci; Tubercle Bacilli; Typhoid; Viruses; etc.
Abortus and Melitense Group: See Undulant Fever
bactericidal action of ultraviolet radiation on air-borne organisms, 56
Bordet-Gengou: See Whooping Cough

Bacteria—Continued
Calmette-Guérin: See Tuberculosis
changes in bacterial cell brought about by action of germicides and antibacterial substances as demonstrated by electron microscope, 487
Coli: See also Bacteria, typhoid group
coli; mode of action of sulfonamides; purines, amino acids, peptones and pancreas as antagonists and potentiators of sulfonamide in E. coli, 240
coli; role of colon organisms and their toxins in epidemic diarrhea of newborn infant, 228
coli; sulfathiazole in treatment of dysenteriform enterocolitis in infants, 152
comparative effectiveness of arsenical compounds and sulfonamide drugs against bacterial infections, 408
comparative therapeutic activity of sulfonamides against bacterial infections in mice, 231
Corynebacteria: See under Diphtheria
culture; sulfanilamide bacteriostasis in presence of mercuric chloride and *p*-aminobenzoic acid, 501
Diphtheria: See under Diphtheria
Dysentery: See Dysentery
Flexner's: See Dysentery
Hemophilus: See Influenza; Whooping Cough
lactic acid group; sulfapyridine bacteriostasis of Lactobacillus arabinosus and its counteraction, 502
Meningococci: See Meningococci
neisseria; isolation of Neisseria flava from genitourinary tract of 3 patients, 487
Paracolon: See Bacteria, typhoid group
pasteurella; sylvatic plague studies; fate of Pasteurella pestis in flea, 313
Pertussis: See Whooping Cough
Pfeiffer's: See Influenza
Salmonella: See Salmonella
Shiga's: See Dysentery
Sonne's: See Dysentery
Streptococci: See Streptococci
subtilis; effect of propylene glycol on bacterial spores, 487
Tuberculosis: See Tubercle Bacilli
Typhoid Group: See also Bacteria, coli; Salmonella; Typhoid; etc.
typhoid group; biochemical and antigenic relationships of paracolon bacteria, 313
typhoid group; susceptibility of Shigella paradysenteriae to sodium sulfathiazole and sulfaguanidine in vitro, with some information regarding Eberthella typhosa, Salmonella paratyphosa, Escherichia coli, Salmonella morgani and proteus, 408
Bactericides: See Germicides
Bacteriophage: See Typhoid
Bacteriostasis: See Bacteria, culture; Bacteria, lactic acid group
Bakwin, H.: Psychogenic fever in infants, *176
Balmis, Francisco Xavier, and introduction of vaccination to Latin America, 229
Bang's Disease: See Undulant Fever
Barbital and Barbital Derivatives, effect on electrical activity of cortex of certain depressant and stimulant drugs: barbiturates, morphine, caffeine, benzedrine and adrenalin, 497
Barbiturates: See Barbital and Barbital Derivatives; Burns
Bardet-Laurence-Biedl Syndrome: See Laurence-Moon-Biedl Syndrome
Basedow's Disease: See Goiter, exophthalmic
Basophilism (Cushing): See Pituitary Body
Bass, M. H.: Deficiency anemia in infants; report of 2 cases, with associated temporary deficiency of antianemic factor in 1 and allergy and abnormal digestion of protein in other, *341
Baumgarten-Cruveilhier Syndrome: See Cruveilhier-Baumgarten Syndrome
Behavior, autonomic nervous system function in children with behavior problems as measured by parotid secretory rate, 237
effect of drugs on behavior and electroencephalograms of children with behavior disorders, 154
psychiatrist and behavior problem, 329
Bell's Palsy: See Paralysis, facial
Benzedrine: See Amphetamine
Benzyl Benzoate: See Scabies
Betaine Compounds; inhibiting effect of methionine, choline and betaine on rabbit's susceptibility to infection with vaccinia, 67
Biedl-Laurence Syndrome: See Laurence-Moon-Biedl Syndrome
Biemond Syndrome: See Laurence-Moon-Biedl Syndrome
Bile, reversibility of quellung reaction and relation between quellung reaction and bile solubility, 56
Birdsong, M.: Influenzal meningitis, *194
Birth Injuries: See Newborn Infants
Premature: See Premature Infants
Weight: See Newborn Infants
Birthmarks, Vascular: See Angioma; Hemangioma
Blackwater Fever, place of quinine in treatment of subtertian malaria, 322
Bladder: See also Urinary Tract
unusual manifestation of lymphatic leukemia, 234
Blatt, M. L.: Epiphysial dysgenesis associated with cretinism in premature infant, *480
Blennorrhea: See Gonorrhea
Blindness: See also Vision, defective
early operation in premature cranial synostosis for prevention of blindness and other sequelae, 419
nutritional degeneration of optic nerve in rats; its relation to tryparsamide amblyopia, 238
Blood: See also Erythrocytes; Hemoglobin and Hemoglobin Compounds; Leukocytes; etc.
absorption, excretion and distribution of penicillin, 501
amino acid studies; plasma amino acid retention, as evidence of impaired liver function; investigations in children with nephrosis and liver disease, 400
amylase activity in disease of carbohydrate metabolism and in nondiabetic pancreatic disease, 411
calcium; disturbed kidney function in newborn infant associated with decreased calcium: phosphorus ratio, 404
calcium; relationship of low blood calcium to parathyroid secretion, 83
Carotene: See also Vitamins, A
carotene; hypervitaminosis A and carotenemia, *33
Cells: See Erythrocytes; Leukocytes
chlorides; experimental and clinical hypochloremia in man, 324
chlorides; severe injury to kidneys and brain following sulfathiazole administration; high serum sodium and chloride levels and persistent cerebral damage, 500
Circulation: See also Capillaries; Cardiovascular Diseases; Cardiovascular System; Heart; etc.
circulation; congenital pulmonary stenosis with closed cardiac septa, 71
circulation time; review of previous methods and introduction of aminophyllin [theophylline ethylenediamine] as new agent, 411
Coagulation: See also Blood, prothrombin
coagulation; production of hypoprothrombinemia and hypocoagulability of blood with salicylates, 494
coagulation; Weltmann reaction in respiratory diseases in children, 73
Diseases: See Anemia; Leukemia; etc.
enzymes; carbonic anhydrase in newborn infants (in relation to cyanosis and blood transfusion), 404
fats and lipoids; effect of pantothenic acid deficiency on blood lipoids of dog, 58
fats and lipoids; influence of vitamin A on serum lipids of normal and deficient rats, 61
fatty acids; studies with dogs maintained on diets low in fat, 314
Fibrin: See Blood, coagulation
Globulin: See Blood, proteins
Groups: See also Agglutinins and Agglutination: Blood, transfusion
groups; erythroblastosis fetalis and blood factor Rh, 317
groups; erythroblastosis fetalis; proposed definition and clarification of term, *445
groups; presence of Rh antibodies in breast milk: further investigations, 401
groups; production of Rh antiserum by inoculation of guinea pigs with human erythrocytes, 494
groups; rapid method for obtaining anti-Rh serum from guinea pigs, 412

Blood—Continued
groups; Rh factor and its application to obstetric practice, 405
groups; Rh factor in relation to jaundice of newborn infant (erythroblastosis fetalis), 404
Injections: See Blood, transfusion
Lipoids: See Blood, fats and lipoids
minimum vitamin A requirements in infants as determined by vitamin A concentration in, 402
phosphatase; serum phosphatase activity and clinical rickets in children in Jerusalem, *348
phosphatase; serum phosphatase values in children showing retardation in osseous development and low metabolic rates, 420
Phospholipids: See Blood, fats and lipoids
phosphorus; disturbed kidney function in newborn infant associated with decreased calcium: phosphorus ratio, 404
phosphorus; urinary excretion and serum concentration of inorganic phosphate in man, 400
Picture: See Blood, groups; Leukocytes
pressure fluctuations in bronchial asthma, 496
pressure, high; blood pressure of adolescents, 494
proteins, effect of adrenal factors on, 82
Prothrombin: See also Blood, coagulation
prothrombin; hemorrhagic disease of newborn, 228
prothrombin; hypoprothrombinemia after salicylate administration in man and rabbits, 412
prothrombin; plasma prothrombin and liver function during sulfonamide therapy, 86
prothrombin; production of hypoprothrombinemia and hypocoagulability of blood with salicylates, 494
prothrombin studies; effect of vitamin K on hypothrombinemia induced by dicumarol [dicoumarin] in man, 234
prothrombin; studies on prothrombin; prothrombinopenic effect of salicylate in man, 495
prothrombin; vitamin K in hemorrhagic disease of newborn infant, 228
prothrombin; vitamin K requirements of newborn, 228
sedimentation; comparison of Westergren and Kato erythrocyte sedimentation rate readings; relation to clinical status of children with rheumatic fever, *474
sedimentation; improved method for determining sedimentation rate of red blood corpuscles, 324
sedimentation; micro-method for estimation of sedimentation rate of red cells, 495
sedimentation rate in school children of federal capital, 325
serum tocopherol; its relation to failure of vitamin E therapy for pseudohypertrophic muscular dystrophy, *371
Sugar: See also Carbohydrates; Dextrose; Diabetes Mellitus; Insulin; etc.
sugar; correlation of extent of tuberculosis with amount of polysaccharide in serum, 323
sugar; effect of tourniquets on venous blood sugar values, 411
sugar in newborn, 228
sugar; role of anterior pituitary in adrenalin hyperglycemia and liver glycogenolysis, 82
therapeutics of sulfonamide compounds; importance of study of their concentration in body, 159
Transfusion: See also Anemia; Blood groups
transfusion; acute laryngotracheobronchitis; treatment of obstructive laryngeal and tracheobronchial edema with hypertonic human plasma; preliminary report, 413
transfusion; carbonic anhydrase in newborn infants (in relation to cyanosis and blood transfusion), 404
transfusion; hemolysins in acute hemolytic anemia, 411
transfusion; hemolytic transfusion reactions due to Rh factor; preventable danger, 71
transfusion; human serum and plasma in diseases of children, 412
transfusion; tolerance of frequent and repeated blood transfusions in children with anemias, 149
Vessels: See Capillaries; Cardiovascular System; Endarteritis; etc.
Bloxsom, A.: Transient paralysis due to bite of American dog tick (Dermacentor variabilis Say), *126
Blumberg, M. L.: Prophylactic value of sulfathiazole against neonatal gonococcic conjunctivitis, *472
Body, Weight: See under Children; Obesity
Bones: See also under names of bones
cyst, 157
Calcification: See Bones, growth
Deformities: See Poliomyelitis; Rickets; etc.
Diseases: See also Osteochondritis; Osteomyelitis; etc.
diseases; polyostotic fibrous dysplasia; review of literature with 2 additional cases, 498
effect of dietary fat on bone calcification in growing rat, 488
growth; epiphysial dysgenesis associated with cretinism in premature infant, *480
growth; menarcheal age and height, weight and skeletal age of girls age 7 to 17, 489
growth; serum phosphatase values in children showing retardation in osseous development and low metabolic rates, 420
marrow; studies in refractory anemia, 412
studies in deposition of lead in bone; calcification and lead deposition, 492
tuberculosis, tuberculin sensitivity in children with, 233
Book Reviews:
Allergy; E. Urbach and P. M. Gottlieb, 504
Allergy, Anaphylaxis and Immunotherapy; B. Ratner, 161
Behind Sulfa Drugs; I. Galdston, 88
Brucellosis in Man and Animals; I. F. Huddleson and others, 161
Convulsive Seizures; T. Putnam, 505
Creatine and Creatinine Metabolism; H. H. Beard, 88
Food You Eat: Practical Guide to Home Nutrition; S. and V. Glasstone, 423
Health and Physical Fitness; I. H. Goldberger and G. T. Hallock, 504
Nicholas Copernicus, 1543-1943; S. P. Mizwa, 423
Principles of Orthodontics; J. A. Salzmann, 335
Puericultura (Higiene alimentare e social da criança); Martagão Gesteira, 335
Rheumatic Fever in Children: Its Recognition and Management, 505
Tables of Food Values; A. V. Bradley, 88
Urology in General Practice; N. F. Ockerblad and H. E. Carlson, 423
Your First Baby; L. C. Glemser, 161
Botallo's Duct: See Ductus Arteriosus
Bougies, fibrous stricture of gullet of 19 years' duration, 414
Bouillaud's Disease: See Rheumatic Fever
Bouquet-Nègre Antigen: See Keratoconjunctivitis
Bourneville-Pringle's Disease: See Sclerosis, tuberous
Bowels: See Intestines
Boyd, J. D.: Dental caries as influenced by fat versus carbohydrate in diet, *278
Braces: See Orthopedics
Brain: See also Cerebellum; Meninges; Nervous System; etc.
abnormalities; hydranencephaly; report of 2 cases which combine features of hydrocephalus and anencephaly, *282
arachnodactyly in 4 siblings with pneumoencephalographic observations of 2, *201
cysts; pubertas praecox in female infant caused by ventricular cyst, 497
Diseases: See also Encephalitis; etc.
diseases; speech disorders and their treatment (relation to diseases of nervous system), 326
effect on electrical activity of cortex of certain depressant and stimulant drugs; barbiturates, morphine, caffeine, benzedrine and adrenalin, 497
electroencephalography; effect of drugs on behavior and electroencephalograms of children with behavior disorders, 154
electroencephalography; symmetric nevi of face, tuberous sclerosis, epilepsy and fibromatous growth on scalp, with abnormal electroencephalograms of members of family, 330
functional development of fetal brain, 236
Inflammation: See Encephalitis
juvenile amaurotic idiocy, 415
oligodendroglioma in infant of 8 months, 498
Sclerosis: See Sclerosis
severe injury to kidneys and brain following sulfathiazole administration; high serum sodium and chloride levels and persistent cerebral damage, 500

Brain—Continued
tumors, diagnosis and prognosis of, 328
tumors in childhood, 78
Bread, vitamin B complex of peeled wheat bread, 315
Breast, Feeding: See Infant Feeding; Milk, human
ganglioneuroma in 5 year old child, *382
Milk: See Infant Feeding; Lactation; Milk, human
relation of mammogenic lobule-alveolar growth factor of anterior pituitary to other anterior pituitary hormones, 155
relation of thyroid to mammary gland structure in rat with reference to male, 155
Bright's Disease: See Nephritis
Bronchi, bronchography in children, 235
Diseases: See Bronchiectasis; Bronchitis; Bronchopneumonia
obstruction and pulmonary atelectasis, 233
Spasm: See Asthma
Bronchial Glands: See Lymph Nodes
Bronchitis and bronchopneumonia, 150
Bronchography: See under Bronchi
Bronchopneumonia: See also Pneumonia
and bronchitis, 150
etiology in infants, 151
Brucellosis: See Undulant Fever
Bruch, H.: Mental development of congenitally hypothyroid children; its relationship to physical development and adequacy of treatment, *205
Brush, J. M.: Initial stabilization of diabetic child, *429
Burns, acrolein and shock; possible relationship of lipoid breakdown products to shock associated with burns, 499
practicable outline for treatment, 159
reduction of fluid loss from damaged (burned) tissues by barbiturate, 499

C T A B: See Ammonia and Ammonium Compounds
Cabbage, availability for human nutrition of vitamin C in raw cabbage and home-canned tomato juice, 402
Caffeine, effect on electrical activity of cortex of certain depressant and stimulant drugs; barbiturates, morphine, caffeine, benzedrine and adrenailn, 497
Calcification: See Bones, growth; Lungs; Teeth; etc.
Calcium and Calcium Compounds, calcium, phosphorus and nitrogen metabolism of young college women, 59
factors influencing retention of nitrogen and calcium in period of growth; calcium and vitamin D requirements of older child, *265
in Blood: See Blood, calcium
interrelationship of calcium, phosphorus and nitrogen in metabolism of preschool children, 58
Therapy: See Tetany
Calmette-Guérin (B C G) Vaccine: See under Tuberculosis
Calorimeter: See Metabolism
Calvin, J. K.: Differential diagnosis of poliomyelitis, 334
Cancer: See also under names of organs and regions in childhood, 86
Canning and Canned Foods, availability for human nutrition of vitamin C in raw cabbage and home-canned tomato juice, 402
Capillaries, occurrence of abnormal capillary fragility in newborn, 403
Carbohydrates: See also Dextrose; Glycogen; Sucrose; Sugar; etc.
dental caries as influenced by fat versus carbohydrate in diet, *278
metabolism; blood amylase activity in disease of carbohydrate metabolism and in nondiabetic pancreatic disease, 411
Carbonic Anhydrase: See Blood, enzymes
Carbuncle, Renal: See Nephritis
Carcinoma: See Cancer; and under names of organs and regions
Cardiovascular Diseases: See also Heart
cardiovascular involvement in congenital syphilis, 410
Cardiovascular System: See also Heart; etc.
cardiovascular and metabolic study of stutterers and non-stutterers, 413
Caries, Dental: See Teeth
Carminatives, effect on emptying time of normal human stomach, 151
Carotene: See Vitamins, A
in Blood: See Blood, carotene
Carotenemia: See Blood, carotene
Carriers: See under Diphtheria; Meningitis; etc.
Cassels, D.: Mycotic endocarditis; report of case with necropsy; review of literature, *128
Catabolism: See Metabolism
Cathartics: See under Phenolphthalein and Phenolphthalein Derivatives
Cavernous Sinus, Thrombosis: See Thrombosis, sinus
Celiac Disease, 87
association of gastrointestinal allergy with celiac syndrome, 328
cause and treatment of, 75
influence of lecithin feeding on fat and vitamin A absorption in man, 401
review of cases of celiac disease in hospital for sick children since outbreak of war, 415
Cells, similarity of cytoplasmic inclusions in infant pneumonitis and bovine epithelial cells, 72
Staining: See Stains and Staining
Cerebellum, abnormalities; congenital anomaly of cerebellar vermis, 153
atrophy, 416
cerebellar syndrome of malarial origin, 233
Cerebrospinal Fever: See Meningitis
Cerebrospinal Fluid: See also Spinal Puncture
Levinson ratio and tryptophan test; comparative value in diagnosis of tuberculous meningitis, *469
Cerebrum: See Brain
Cetavlon: See Ammonia and Ammonium Compounds
Cetyl Trimethyl Ammonium Bromide: See Ammonia and Ammonium Compounds
Cevitamic Acid: See Ascorbic Acid
Chafing: See Intertrigo
Chandler, A. C.: Transient paralysis due to bite of American dog tick (Dermacentor variabilis Say), *126
Character education in childhood and youth, 417
Chauffard-Still Disease: See Arthritis deformans
Cheese, value of dairy products in nutrition, 488
Chemotherapy: See under names of diseases and chemotherapeutic agents, as Communicable Diseases; Meningitis; Sulfonamides; etc.
Chest: See Thorax
Chiasm, Optic: See Optic Chiasm
Chickenpox, varicella following exposure to herpes zoster, 491
Child Labor and school attendance in United States, 403
Child Welfare: See also Infant Welfare
assistance to abandoned and delinquent child should be integratedly technical, 402
boarding homes, 144
developments in social assistance to children in Uruguay, 490
eighth Pan-American Child Congress; its projection in America, 87
extradition of minors; means for its development and revision of its present idea from point of view of right of guardianship of minors, 63
law in behalf of social defense for children, 490
medical social protection of premature child, 490
necessity of introducing teaching of family pedagogy into higher grades of primary schools, into secondary schools, into normal schools for women and into maternity schools, 62
progress in development of economic and social services for families and children, 490
progress in development of services for education and recreation, 316
protection of children in danger zones and planning for care of children after evacuation arising from military necessity, 316
ten years of work in Uruguay, 403
Children: See also Infants; Newborn Infants; Pediatrics; Schools; etc.
affectivity and growth in, 489
Children's Memorial Hospital, Chicago, 88
Crippled: See Cripples
Delinquent: See Delinquency
diseases of, 87
Growth: See Growth
height and weight measurements of school children, 316
human serum and plasma in diseases of, 412
mental development of congenitally hypothyroid children; its relationship to physical development and adequacy of treatment, *205

Children—Continued
morbid psychologic states associated with physical disabilities, 81
Nervous and Mental Disabilities: See Nervous and Mental Disabilities
Nutrition: See Diet and Dietetics; Nutrition; Schools; etc.
protection in danger zones and planning for care after evacuation arising from military necessity, 316
Chlorides, effect of chloride with high and low iodine supply on thyroid gland of rat, 419
in Blood: See Blood, chlorides
Choanae: See Nose
Cholera, Infantile: See Diarrhea
Cholesterol: See Lipoids
Choline and Choline Derivatives: See also Bile
inhibiting effect of methionine, choline and betaine on rabbit's susceptibility to infection with vaccinia, 67
Chondroma, solitary, and chondromatosis, 157
Choriomeningitis, relationship between benign lymphocytic meningitis and poliomyelitis, 320
Chorioretinitis: See Retinochoroiditis
Christian-Weber's Disease: See Panniculitis
Ciliary Body: See Uvea
Circulation: See Blood, circulation
Circulatory System: See Blood, circulation; Cardiovascular System
Clatworthy, H. W., Jr.: Development and growth of human embryo and fetus; graphic representation of some aspects, *167
Climate, menarche in relation to, 155
Cold: See also Temperature
spirochetal survival in frozen plasma, 70
Colds: See Respiratory Tract, diseases
Colic, Lead: See Lead, toxicity
Collodion Disease: See Ichthyosis
Colon: See also Gastrointestinal Tract; Intestines; Sigmoid
in healthy newborn infant, 77
Invagination: See Intussusception
Colostrum: See also Infant Feeding
as source of diphtheria antitoxin in actively immunized pregnant mothers, 318
Coma: See under Diabetes Mellitus
Communicable Diseases: See also Immunity; Measles; Meningitis; Syphilis; etc.
clinical experience with certain chemotherapeutic agents in treatment of various infectious diseases of childhood, 65
discussion on prophylaxis of acute specific fevers, 407
influence of social conditions on diphtheria, measles, tuberculosis and whooping cough in early childhood in London, 232
myocarditis in contagious and infectious diseases, *296
studies on air-borne infection in hospital ward; effect of ultraviolet light on cross-infection in infants' ward, 66
Complement and ascorbic acid; study of their relationship, 315
Conjunctiva, slit lamp microscope in nutrition surveys, 227
Conjunctivitis: See also Keratoconjunctivitis
encephalitis following inclusion conjunctivitis, 228
prophylactic value of sulfathiazole against neonatal gonococcic conjunctivitis, *472
Contagious Diseases: See Communicable Diseases
Convalescent Serum: See Measles; etc.
Convulsions: See also Epilepsy; Tetany; etc.
anticonvulsant action of diphenylhydantoin and some related compounds, 78
in infants, 153
Cooley's Anemia: See Anemia, erythroblastic
Cooperstock, M.: Atelectasis complicating acute poliomyelitis with involvement of respiratory muscles, *457
Cornea, Inflammation: See Keratoconjunctivitis
nodular keratitis, 157
slit lamp microscope in nutrition surveys, 227
Corynebacteria: See under Diphtheria
Coryza: See Respiratory Tract, diseases
Coumarin, prothrombin studies; effect of vitamin K on hypothrombinemia induced by dicumarol [dicoumarin] in man, 234
Cranium, early operation in premature cranial synostosis for prevention of blindness and other sequelae, 419
effect of bone dysplasia on cranial nerves in vitamin A deficient animals, 315
fatal intracranial venous hematoma following ventricular drainage, 153
vibration of thorax by percussion of skull and patella, 159
Cretinism, 87
epiphysial dysgenesis associated with cretinism in premature infant, *480
mental development of congenitally hypothyroid children; its relationship to physical development and adequacy of treatment, *205
Crime and Criminals: See Delinquency
Cripples, morbid psychologic states associated with physical disabilities, 81
Cruveilhier-Baumgarten Syndrome in infant, 415
Crying, clinical importance of Sisto's sign in early diagnosis of congenital syphilis, 148
Cryptorchidism: See Testes, undescended
Crystalline Lens: See Lens, Crystalline
Culture Mediums: See under Bacteria; etc.
Curare, fatal effects of prolonged complete curarization, *360
Cushing's Syndrome: See Pituitary Body
Cyanosis, carbonic anhydrase in newborn infants (in relation to cyanosis and blood transfusion), 404
Cystine and Cysteine, nitrogen balance in experimental human deficiencies of methionine and cystine, 314
Cysts: See under names of organs and regions, as Bones; Brain; Liver; etc.
Cytoplasm: See Cells

Dactyloscopy: See Fingerprints
Daly, M. M. I.: Roentgenograms of chest taken during pertussis, *463
Dark Adaptation: See Eyes, accommodation and refraction
David, J. K., Jr.: Tularemic meningitis; report of case and summary of previously reported cases, *44
Deaf-Mutism, intelligence tests for deaf-mutes, 327
Death, certification in infancy, 62
Rate: See Infant Mortality
sudden, in diphtheria, 318
sudden, in infancy, 160
Defectives: See also Cripples; Nervous and Mental Disabilities
physically handicapped persons and employment, 62
Deficiency Diseases: See Diet and Dietetics; Nutrition; Vitamins; etc.; and under names of various diseases
Deformities: See under names of organs and regions
Dehydration, reduction of fluid loss from damaged (burned) tissues by barbiturate, 499
secretion of urine by dehydrated and normal infants, 154
7-Dehydrocholesterol: See Rickets
Delinquency, assistance to abandoned and delinquent child should be integratedly technical, 402
irresponsibility of juvenile delinquents, 237
Dentin: See Teeth
Dentistry: See also Teeth
dental services for school children of interior; ideas on organization and function of dentistry among school children, 500
importance of orthodontia in pediatrics, 159
Dentition: See Teeth
Dermacentor: See Ticks
Dermatitis: See also Eczema; etc.
and eczema, 239
Hemorrhagic: See Purpura
Medicamentosa: See under names of drugs
on synthetic ration adequate for growth and reproduction in rat, 314
Rhus: See Rhus, poisoning
Dermatomyositis, 156
Dermatophytosis: See under Ringworm
De Sanctis, A. G.: Relapsing febrile nodular nonsuppurative panniculitis (Weber-Christian disease); review of literature, with report of case, *120

Desoxycorticosterone Acetate: See Adrenal Preparations
Dextrose: See also Blood, sugar; Carbohydrates; Sugars
effect of glucose and sucrose on respiratory quotient and muscular efficiency of exercise, 58
Dhayagude, R. G.: Erythroblastic anemia of Cooley (familial erythroblastic anemia) in Indian boy, *290
Diabetes Insipidus and diuresis of 10 liters in child, 156
antagonism of pitressin and adrenal cortical extracts in human diabetes insipidus, 83
relationship of thyroid to polyuria of experimental diabetes insipidus, 419
Diabetes Mellitus: See also Blood, sugar
case in early childhood, 156
course of measles in, 148
dental caries as influenced by fat versus carbohydrate in diet, *278
initial stabilization of diabetic child, *429
ketosis in relation to hepatic reserves of glycogen; study of normal and of diabetic children, *100
use of insulin in its various forms in treatment, 155
vitamin deficiencies in diabetic children, 155
Diadokokinesis: See Movements
Diaphragm, hernias and eventrations of, 497
Diarrhea: See also Dysentery
epidemiology in New York city, 151
hospital diarrhea, 496
infectious factor in infantile cholera; treatment by sulfapyridine, 152
recurrent and chronic, in infancy and childhood, *139
role of colon organisms and their toxins in epidemic diarrhea of newborn infant, 228
sulfaguanidine in neonatal epidemic gastroenteritis, 414
treatment in infancy, 77
Diathermy: See under names of diseases, organs and regions
Diathesis, Allergic: See Anaphylaxis and Allergy; Asthma
Hemorrhagic: See also Hemophilia; Purpura; etc.
hemorrhagic, modern concepts of classification of, 149
Dick Test: See Scarlet Fever
Dicoumarin: See Coumarin
Diet and Dietetics: See also Food; Infant Feeding; Nutrition; Vitamins; under names of various diseases, as Diabetes Mellitus; and under names of foods, as Bread; Cabbage; Milk; etc.
effect of diet in rats on adrenal weights and on survival following adrenalectomy, 418
initial stabilization of diabetic child, *429
nutritive adequacy of certain low-cost food mixtures, 401
relation of maternal diet to breast feeding, 225
Teeth and Diet: See under Teeth
Digestive System: See also Gastrointestinal Tract; Intestines; Pancreas; Stomach; etc.
digestibility of some animal and vegetable fats, 401
Dihydrotachysterol, Therapy: See Rickets
Dilantin Sodium Therapy: See Epilepsy
Diphenylhydantoin: See Convulsions
Diphtheria, bacteriology and epidemiology in Brazil; vaccination, 231
colostrum as source of diphtheria antitoxin in actively immunized pregnant mothers, 318
immunization in England and Wales, 231
in year 1941, 231
influence of social conditions on diphtheria, measles, tuberculosis and whooping cough in early childhood in London, 232
laryngotracheobronchial, 407
myocarditis in, *297
prophylaxis, 87
Schick reactions and diphtheria immunization of South African Field Hospital Staff in Middle East, 407
Schick test reactions and serum antitoxin titers after injections of toxoid, 64
sudden death in, 318
use of diphtheria anatoxin for carriers of virulent strains of Loeffler's bacillus, 147
Diphyllobothrium: See Tapeworm Infection
Diplegia: See Paralysis
Directory of Medical Specialists, 503
of pediatric societies, 162, 242, 336, 424, 506
Disk, Intervertebral: See under Spine
Optic: See Nerves, optic
Dislocations: See under names of joints, as Hip; etc.
Distemper, factors in preservation of virus, 57
Diuresis and Diuretics: See also Diabetes Insipidus; Kidneys; Water, metabolism; etc.
diabetes insipidus and diuresis of 10 liters in child, 156
Diverticula: See under Brain; Intestines; etc.
Drayer, C.: Arachnodactyly in 4 siblings with pneumoencephalographic observations of 2, *201
Drugs: See also under names of individual drugs and under names of diseases
effect on electrical activity of cortex of certain depressant and stimulant drugs; barbiturates, morphine, caffeine, benzedrine and adrenalin, 497
Ductus Arteriosus: See also Heart, abnormalities
diagnosis and evaluation of compensated and uncompensated patency of, 324
patency in adults, 324
patent, complicated by subacute bacterial endarteritis treated by ligature of ductus, 325
results of surgical treatment of patency of ductus arteriosus complicated by subacute bacterial endarteritis, 324
Duodenum, effect of hydrochloric acid on pyloric sphincter, on adjacent portions of digestive tract and on process of gastric evacuation, 75
Ulcer: See Peptic Ulcer
Dust, beta hemolytic streptococci isolated from public room floors, 57
source of allergic activity of house dust, 420
Dwarfism: See also Cretinism
hypophysial dwarfing, 156
Dysentery: See also Diarrhea
acute diarrheal diseases; cultural observations on relative efficacy of sulfonamides in Shigella dysenteriae infections, 414
acute diarrheal diseases; typing of Shigella dysenteriae Flexner, 414
Amebic: See Amebiasis
bacillary, 232
bacillary, caused by Bacterium dysenteriae P274, 409
bacillary; effect of oral administration of sulfanilylguanidine on experimental bacillary dysentery in isolated loops of colon of Macaca mulatta and effect when introduced into loops, 320
bacillary; some results and conclusions from series of patients treated with sulfaguanidine, 409
dysenteries, 319
effect of sulfathiazole in treatment, 321
Flexner, 321
prophylactic use of sulfanylguanidine in outbreak, 321
sulfathiazole in treatment of dysenteriform enterocolitis in infants, 152
Dysostosis: See Bones, growth
Dysplasia: See under Cranium
Polyostotic Fibrous: See Bones, diseases
Dyspnea: See also Asthma
fatal case of tachycardia in infant, 234
Dystrophy, Adiposogenital: See Laurence-Moon-Biedl Syndrome; Pituitary Body
in Infants: See under Nutrition
muscular; electrocardiogram in familial muscular dystrophy, 156
muscular; serum tocopherol; its relation to failure of vitamin E therapy for pseudohypertrophic muscular dystrophy, *371
muscular; treatment of diseases of muscle, 238

Ear: See also Mastoid; Otorhinolaryngology; etc.
discharge; chronic otorrhea due to food sensitivity, 234
Diseases: See Meningitis; Otitis Media
Earache; common causes and probable nerve pathways, 326
Eberthella: See Typhoid
Ectromelia, Infectious; studies on air-borne virus infections, 321
Eczema, allergy to food odors; its relation to management of infantile eczema, 421
and dermatitis, 239

Eczema—Continued
infantile; complications caused by virus of herpes simplex; description of clinical characteristics of unusual eruption and identification of associated filtrable virus, *247; correction, 503
infantile; use of vitamin B complex in treatment, 331
infantile, vitamin A absorption in, 422
Edema: See under Lungs; Respiratory Tract; Thorax; etc.
Education and Training: See under Children; Schools
Eitzen, O.: Pulmonary hemosiderosis in 6 year old boy; clinical and pathologic report, *387
Electrocardiogram: See under Heart
Electrocoagulation: See under specific headings
Electroencephalography: See Brain, electroencephalography
Embryology: See also Fetus; Monsters; and under names of special organs and structures
development and growth of human embryo and fetus; graphic representation of some aspects, *167
Emotions, study of emotions and mental states in infants, 154
Emphysema, obstructive, and atelectasis in tuberculosis of infants and children, 323
pneumatocele, or localized bullous emphysema following pneumonia, 414
Empyema, chronic, treatment of, 327
Encephalitis: See also Encephalomyelitis
fetal toxoplasmic encephalitis; type of congenital cerebral disease, 78
following inclusion conjunctivitis, 228
mosquito vectors and inapparent animal reservoirs of St. Louis and western equine encephalitis viruses, 487
relation of neurotropic streptococci to encephalitis and encephalitic virus, 236
Encephalography: See under Brain
Encephalomyelitis and multiple sclerosis, 497
discussion on recent experiences of acute encephalomyelitis and allied conditions, 417
equine, sequels of, 415
isolation and properties of equine virus (Eastern strain), 313
mosquito vectors and inapparent animal reservoirs of St. Louis and western equine encephalitis viruses, 487
scarlatinal, 230
western equine, in infants, 416
Endameba Histolytica: See Amebiasis
Endarteritis, patent ductus arteriosus complicated by subacute bacterial endarteritis treated by ligature of ductus, 325
results of surgical treatment of patency of ductus arteriosus complicated by subacute bacterial endarteritis, 324
Endocarditis, congenital subaortic stenosis, with deformity of aortic valve, 494
endocardial fibroelastosis (so-called fetal endocarditis); report of 2 cases occurring in siblings, 411
mycotic; report of case with necropsy; review of literature, *128
myocarditis associated with, *304
Rheumatic: See under Rheumatic Fever
Endocrine Glands: See Hormones; Metabolism; and under names of glands
Endocrine Therapy: See under names of glands and hormones, as Adrenal Preparations; Insulin; Pituitary Preparations; Thyroid; etc.
Energy Exchange: See Metabolism
Enteritis: See Diarrhea; Dysentery; Gastrointestinal Tract; Intestines, diseases; etc.
Enterobiasis: See Oxyuriasis
Enterocolitis: See Dysentery; Intestines
Enuresis: See Urination, incontinence
Enzymes: See Blood, enzymes; Pancreas; and under names of enzymes
Eosinophils: See also Leukocytes
experimental eosinophilia with keratin from Ascaris suum and other sources, 65
relationship of eosinophil response to factors involved in anaphylaxis, 239
Epidermis: See Skin
Epidermolysis bullosa hereditaria; case for diagnosis, 422
Epilepsy: See also Convulsions; Sclerosis, tuberous
mebaral (methylethylphenobarbital) in treatment, 153
prevention and treatment of convulsive disorders, 236
pseudojacksonian, in children, 328
relationship between infantile enuresis and epileptic crisis, 81
symmetric nevi of face, tuberous sclerosis and fibromatous growth on scalp, with abnormal electroencephalograms of members of family, 330
Epilola: See Sclerosis, tuberous
Epinephrine: See Adrenal Preparations
Epiphyses, epiphysial dysgenesis associated with cretinism in premature infant, *480
tetany due to deficiency in magnesium; its occurrence in child of 6 years with associated osteochondrosis of capital epiphysis of femur (Legg-Perthes disease), *117
Epstein, H. C.: Levinson ratio and tryptophan test; comparative value in diagnosis of tuberculous meningitis, *469
Equilibrium, Acid-Base: See Acid-Base Equilibrium
Ergot: See Urination, incontinence
Erythema infectiosum; report of extensive epidemic, 420
nodosum, 158
nodosum; histopathology of Mantoux reaction and erythema nodosum, 148
Erythredema: See Acrodynia
Erythroblastosis: See Anemia, erythroblastic
Erythroblastosis, Fetal, and blood factor Rh, 317
presence of Rh antibodies in breast milk; further investigations, 401
proposed definition and clarification of term, *445
Rh factor in relation to jaundice of newborn infant, 404
Erythrocytes: See also Anemia; Hemoglobin and Hemoglobin Compounds; Hemolysis; etc.
effects of hormones on erythropoiesis in hypophysectomized rat, 83
formation of red blood corpuscles, 412
production of Rh antiserum by inoculation of guinea pigs with human erythrocytes, 494
Sedimentation: See Blood, sedimentation
studies in anemias of infancy and early childhood, 495
Erythrodermia, Ichthyoid: See Ichthyosis
Erythropoieses: See Erythrocytes
Esophagus, fibrous stricture of gullet of 19 years' duration, 414
Evacuation: See War
Exanthems: See Communicable Diseases; and under names of exanthematous diseases
Exercise, effect of glucose and sucrose on respiratory quotient and muscular efficiency of, 58
tolerance test as measure of chronic fatigue in children, 331
Exomphalos: See Hernia, umbilical
Exophthalmos: See Goiter, exophthalmic
Exsiccosis: See Dehydration
Extremities: See Arms; etc.
Paralysis: See Poliomyelitis
Eyes: See also Vision; and under names of special structures and diseases
abnormalities; rare congenital ocular abnormality, 238
accommodation and refraction; testing dark adaptation, 489
Diseases: See Glaucoma; etc.
molluscum contagiosum of, 499
paralysis; congenital paralysis of lateral rotators of eyes with paralysis of muscles of face, 416

Face Masks: See Masks
Paralysis: See Paralysis, facial
symmetric nevi of face, tuberous sclerosis, epilepsy and fibromatous growth on scalp, with abnormal electroencephalograms of members of family, 330
Fat: See also Lipoids
body fats in rat acrodynia, 84
comparative nutritive value of butter fat and vegetable oils, 488
dental caries as influenced by fat versus carbohydrate in diet, *278

Fat—Continued
digestibility of some animal and vegetable fats, 401
effect of dietary fat on bone calcificaton in growing rat, 488
excretion by normal children, 401
in Blood: See Blood, fats and lipoids
influence of lecithin feeding on fat and vitamin A absorption in man, 401
studies with dogs maintained on diets low in fat, 314
Fatigue, exercise tolerance test as measure of chronic fatigue in children, 331
Feces, effect of sodium citrate administration on excretion of lead in urine and feces, 331
fat excretion by normal children, 401
Feeblemindedness: See Idiocy; Laurence-Moon-Biedl Syndrome
Fear's Disease: See Acrodynia
Femur: See also Hip
Epiphyses: See Epiphyses
treatment of femoral shaft fractures in infants, 159
Ferrebee, J. W.: Subclinical vitamin deficiency; thiamine in skeletal muscle of infants and children, *30
Fertility: See Reproduction
Fetus: See also Embryology; Labor; Monsters; Pregnancy
Asphyxia: See Asphyxia
causes of fetal and neonatal death, 404
development and growth of human embryo and fetus; graphic representation of some aspects, *167
endocardial fibroelastosis (so-called fetal endocarditis); report of 2 cases occurring in siblings, 411
excretion of ketosteroids in human pregnancy urine in relation to sex of, 403
fetal myocarditis, *296
fetal toxoplasmic encephalitis; type of congenital cerebral disease, 78
Injuries: See Newborn Infants
Pathology: See Hydrocephalus
Fever: See also Malaria; Temperature; Typhoid; Undulant Fever; etc.
Cerebrospinal: See Meningitis
depression of gastric motility without elevation of body temperature following injection of pyrogens, 74
discussion on prophylaxis of acute specific fevers, 407
Malta: See Undulant Fever
psychogenic, in infants, *176
relapsing febrile nodular nonsuppurative panniculitis (Weber-Christian disease); review of literature, with report of case, *120
Therapeutic: See Gonorrhea; Neurosyphilis; Poliomyelitis; Undulant Fever
Undulant: See Undulant Fever
Fibroadenoma, large solitary bile-cell fibroadenoma of liver, 76
Fibroma, Riga-Fede disease, 152
symmetric nevi of face, tuberous sclerosis, epilepsy and fibromatous growth on scalp, with abnormal electroencephalograms of members of family, 330
Fingerprints, dactyloscopy in identification of newborn infants, 229
Fingersucking, serial dental study from birth to 5 years, 159
Fingers and Toes, Abnormalities: See Arachnodactylia
Flavicin: See Aspergillus
Fleas: See Plague
Floors, Dust: See Dust
Flour: See Bread
Fluids, innovation in fluid diet in infancy, 226
Fluorides, caries-fluorine hypothesis and suggested study to test its application, 500
domestic water and dental caries, 85
endemic fluorosis in Great Britain, 401
fluorine distribution, 315
outbreak of acute fluoride poisoning, 314
Fluorine: See Fluorides
Fluoroscopy: See under Roentgen Rays
Fluorosis: See Fluorides
Food: See also Diet and Dietetics; Nutrition; Vitamins; and under names of various foods, as Bread; Cabbage; Fruit and Vegetables; Milk; etc.
allergy; allergy to food odors; its relation to management of infantile eczema, 421
allergy; association of gastrointestinal allergy with celiac syndrome, 328
allergy; chronic otorrhea due to food sensitivity, 234
allergy; hemolysins in acute hemolytic anemia, 411
allergy; roentgen observations on children with gastrointestinal allergy to foods, 421
allergy, sensitization to fresh fruits; clinical and experimental observations, 84
Canned: See Canning and Canned Foods
nicotinic acid in, 61
Poisoning: See also Salmonella
poisoning; antigenic structure of bacteria incriminated in 3 unrelated outbreaks of food infection, 57
Forceps: See Labor
Foreign Bodies: See under names of organs and regions
Fractures: See under Femur; etc.
Frank, H. E.: Serum tocopherol; its relation to failure of vitamin E therapy for pseudohypertrophic muscular dystrophy, *371
Friderichsen-Waterhouse Syndrome: See Adrenals, hemorrhage
Fruits and Vegetables: See also under names of fruits and vegetables, as Cabbage; Oranges; Peaches; Tomatoes; etc.
nicotinic acid content of common fruits and vegetables as prepared for human consumption, 315
studies in food allergy; sensitization to fresh fruits; clinical and experimental observations, 84
Fungi: See Actinomycosis; Moniliasis; Mycosis; Ringworm; etc.

Ganglioneuroma of breast in 5 year old child, *382
Garrison, Harvey F., new appointment for, 88
Gastric Acidity: See under Stomach
Juice: See under Stomach
Ulcer: See Peptic Ulcer
Gastroenteritis: See Gastrointestinal Tract
Gastrointestinal Tract: See also Colon; Digestive System; Duodenum; Intestines; Stomach; etc.
cream-filled pastry source of infection, 414
incidence and mortality of breast and artificially-fed infants admitted to hospital with infections, 225
infection and therapy with sulfonamide compounds in cases of gastrointestinal disorder and enteritis of infancy, 77
milk-borne outbreak of gastroenteritis in Oklahoma City, 77
nitrogen storage following intravenous and oral administration of casein hydrolysate to infants with acute gastrointestinal disturbance, 400
normal stomach and small intestine in infant, 76
roentgen observations on children with gastrointestinal allergy to foods, 421
secretion of urine by dehydrated and normal infants, 154
specific prophylaxis against enteric diseases, 327
Gee's Disease: See Celiac Disease
Genitals: See Genitourinary Tract; Urinary Tract; and under names of genitals, as Testes; etc.
Genitourinary Tract: See also Urinary Tract; and under organs of genitourinary tract
isolation of Neisseria flava from genitourinary tract of 3 patients, 487
similar urogenital anomalies in identical twins, *199
surgical intervention for congenital malformations of, 238
Germicides: See also Gramicidin; Sterilization, surgical
changes in bacterial cell brought about by action of germicides and antibacterial substances as demonstrated by electron microscope, 487
in vivo method for evaluation of germicidal substances used for skin disinfection, 85

Giardiasis: See Lambliasis
von Gierke's Disease: See under Glycogen
Glands: See under names of glands, as Adrenals; Lymph Nodes; etc.
Glaucoma, congenital, operation for, 157
Gleich, M.: Prophylactic value of sulfathiazole against neonatal gonococcic conjunctivitis, *472
Globulin in Blood: See Blood, proteins
Glomerulonephritis: See Nephritis
Glucose: See Dextrose
Glycemia: See Blood sugar
Glycogen, ketosis in relation to hepatic reserves of glycogen; study of normal and of diabetic children, *100
role of anterior pituitary in adrenalin hyperglycemia and liver glycogenolysis, 82
von Gierke's disease (glycogenosis); report of case, 152
Glycogenosis: See under Glycogen
Goiter, exophthalmic, of juvenile type, 155
sporadic congenital obstructive goiter with recovery following operation in 13 day old infant, 419
Gonadotropins: See also Pituitary Body; Pituitary Preparations
cryptorchidism, 329
Gonads: See Ovary; Testes
Gonococci, Infections: See under Gonorrhea
Gonorrhea, fever therapy, 501
prophylactic value of sulfathiazole against neonatal gonococcic conjunctivitis, *472
Goodfriend, J.: Epiphysial dysgenesis associated with cretinism in premature infant, *480
Gramicidin, mode of action of gramicidin and penicillin in treatment of infections, 320
Graves' Disease: See Goiter, exophthalmic
Gravidity: See Pregnancy
Greenbaum, J.: Roentgenograms of chest taken during pertussis, *463
Greene, M.: Pneumococcic meningitis; complete recovery of 6 month old infant treated with penicillin, *485
Grip: See Influenza
Gross, R.: Subclinical vitamin deficiency; thiamine in skeletal muscle of infants and children, *30
Growth: See also Diet and Dietetics; Embryology; Nutrition; etc.
and affectivity in children, 489
dermatitis on synthetic ration adequate for growth and reproduction in rat, 314
effect of aromatic hydrocarbons on growth; reversible inhibition of pantothenic acid by sulfapyridine, 489
factors influencing retention of nitrogen and calcium in period of growth; calcium and vitamin D requirements of older child, *265

Haemophilus Pertussis: See Whooping Cough
Handicapped: See Defectives
Hansen, Arild E., new appointments for, 241
Hay Fever: See also Anaphylaxis and Allergy; Rhinitis
Kochia scoparia as factor in inhalant allergy, 331
sensitivity to ailanthus pollen, 421
studies on blocking antibody in serum of ragweed-treated patients; search for inhibiting substances in other types of immune serum, 421
Head: See also Cranium
injuries; principles of treatment of closed head injury, 331
Heart: See also Blood, circulation; Cardiovascular System; and under names of various conditions, as Rheumatic Fever; etc.
Abnormalities: See also Ductus Arteriosus; etc.
abnormalities; congenital pulmonary stenosis with closed cardiac septa, 71
abnormalities; persistent common atrioventricular ostium in child with mongolism, 149
abnormalities; relationship of congenital heart disease to premature birth, 411
acute cardiac insufficiency in infant; report of case, 149
Diseases: See Cardiovascular Diseases; Endocarditis; Myocarditis; etc.
Diseases, Congenital: See Heart, abnormalities
electrocardiogram in familial muscular dystrophy, 156
electrocardiogram of Cushing's syndrome, 155
Heart—Continued
electrocardiographic variations in acute glomerulonephritis, *106
rate; fatal case of tachycardia in infant, 234
Rheumatic Disturbances: See Rheumatic Fever
Valves: See under names of valves, as Aortic Valve; etc.
Heat: See also Temperature
Production: See Metabolism
radiant, and comfort, 62
Height: See also under Growth
and weight measurements of school children, 316
Heine-Medin Disease: See Poliomyelitis
Heliotherapy and Phototherapy: See under names of various organs and diseases
Hemangioma of arm causing delay in delivery and neonatal death, 404
Hematology: See Blood
Hematoma: See under Cranium
Hemiplegia in tuberculous meningitis, 233
Hemochromatosis, pulmonary hemosiderosis in 6 year old boy; clinical and pathologic report, *387
Hemoclastic Crisis, Mester's test in diagnosis of rheumatic disease of children, 233
Hemoglobin and Hemoglobin Compounds: See also Anemia; Blood; Erythrocytes; Hemoglobinuria; Hemolysis; etc.
deficiency anemia in infants; report of 2 cases, with associated temporary deficiency of antianemic factor in 1 and allergy and abnormal digestion of protein in other, *341
pulmonary hemosiderosis in 6 year old boy; clinical and pathologic report, *387
studies in anemias of infancy and early childhood, 495
Hemoglobinuria: See also Blackwater Fever
chronic hemolytic anemia with paroxysmal nocturnal hemoglobinuria (Marchiafava-Micheli syndrome); report of case with marked thrombocytopenia in 5 year old child, 324
Hemolysin: See under Anemia; Hemolysis
Hemolysis: See also Anemia, hemolytic; Erythroblastosis, Fetal; Erythrocytes
hemolytic transfusion reactions due to Rh factor; preventable danger, 71
Hemophilia: See also Diathesis, hemorrhagic
modern concepts of classification of hemorrhagic diathesis, 149
Hemophilus: See Influenza; Whooping Cough
Hemopoietic System: See Blood; Erythrocytes; Leukocytes
Diseases: See Anemia; Erythroblastosis, Fetal; Leukemia; etc.
Hemoptysis, hemorrhage from trachea, bronchi and lungs of nontuberculous origin, 72
Hemorrhage: See also Adrenals, hemorrhage; Blood, coagulation; Hemophilia; Hemostasis; Meninges; Purpura, hemorrhagic; Tonsillectomy; etc.
hemorrhagic diseases of newborn, 228
vitamin K and neonatal hemorrhage, 87
Hemosiderosis: See Hemochromatosis
Hemostasis: See also Blood, coagulation; etc.
effect of tourniquets on venous blood sugar values, 411
Henoch-Schönlein Purpura: See Purpura
Hernia and eventrations of diaphragm, 497
umbilical; exomphalos successfully treated by operation, 152
Herpes, effect of temperature on growth and survival of myxoma, herpes and vaccinia viruses in tissue culture, 56
simplex, complications of infantile eczema caused by virus of; description of clinical characteristics of unusual eruption and identification of associated filtrable virus, *247; correction, 503
zoster, varicella following exposure to, 491
Herter-Gee Disease: See Celiac Disease
Hindus, erythroblastic anemia of Cooley (familial erythroblastic anemia) in Indian boy, *290
Hip: See also Femur
congenital dislocation, 499
Histamine, antibodies to histamine induced in human beings by histamine conjugates, 420
Holmes, A. D.: Ascorbic acid, riboflavin and thiamine content of cow's milk; influence of ration, *376

Hormones: See also Adrenal Preparations: and under names of organs, as Insulin; Ovary; Pituitary Body; etc.
effect on erythropoiesis in hypophysectomized rat, 83
Gonadotropic: See Gonadotropins
Sex: See Pituitary Preparations; Pregnancy, urine in; und under names of organs, as Ovary; Pituitary Body; Testes; etc.
Thyrotropic: See Pituitary Preparations
Hospitals, artificial feeding of healthy infants in, 59
diarrhea, 496
Flexner dysentery, 321
prophylactic use of sulfanylguanidine in dysentery outbreak, 321
psychogenic fever in infants, *176
review of cases of celiac disease in hospital for sick children since outbreak of war, 415
rheumatic infections in Cincinnati hospitals; study of 3,475 admissions from 1930 to 1940; comparison with incidence in Philadelphia hospitals from 1930 to 1934, *182
studies on air-borne infection in hospital ward; effect of ultraviolet light on cross-infection in infants' ward, 66
studies on air-borne infection in hospital ward; effects of ultraviolet irradiation and propylene glycol vaporization on prevention of experimental and air-borne infection of mice by droplet nuclei, 66
Hulse, M. C.: Subclinical vitamin deficiency; thiamine in skeletal muscle of infants and children, *30
Hurtado y Galtés, publication in honor of, 335
Hydranencephaly: See Brain, abnormalities
Hydrocarbons, effect of aromatic hydrocarbons on growth; reversible inhibition of pantothenic acid by sulfapyridine, 489
Hydrocephalus, hydranencephaly; report of 2 cases which combine features of hydrocephalus and anencephaly, *282
Hydrogen Ion Concentration: See Acid-Base Equilibrium; Acidosis; etc.
Hyperglycemia: See Blood, sugar
Hyperlipemia: See Blood, fats and lipoids
Hypermetropia: See Hyperopia
Hyperopia, problem of hypermetropic miner, 330
Hyperpyrexia: See Fever
Hypertension: See Blood pressure, high
Hyperthermia: See Fever
Hypertrophy: See under names of organs and regions, as Adrenals; etc.
Hypocalcemia: See Blood, calcium
Hypogenitalism: See Laurence-Moon-Biedl Syndrome
Hypoglycemia: See Blood, sugar; Diabetes Mellitus
Hypophysis: See Pituitary Body
Hypoprothrombinemia: See Blood, prothrombin
Hypothyroidism: See under Thyroid
Hypoxia: See Oxygen, deficiency

Ichthyosis, congenital, 85
Icterus: See Jaundice
Idiocy, juvenile amaurotic, 415
Mongolian: See Mongolism
some anomalous forms of amaurotic idiocy and their bearing on relationship of various types, 417
Ileitis: See under Intestines
Ileum: See Intestines; Intussusception
Ilex Paraguayensis: See Maté
Imbecility: See Idiocy
Immunity: See also under Anaphylaxis and Allergy; Diphtheria; Parotitis; etc.
attitude of nation toward immunization procedures, 491
mixed immunization in infancy and childhood, 406
resistance to diseases in childhood, 502
Inanition: See Nutrition
Indians: See Hindus
Industry: See also Child Labor; Mines and Miners; etc.
physically handicapped persons and employment, 62
Infant Feeding: See also Diet and Dietetics; Nutrition; Vitamins; and under names of various foods, as Milk; etc.
artificial feeding of healthy infants, 60
artificial feeding of healthy infants in hospitals, 59
economic and social aspects of artificial feeding in program of infant welfare protection in Buenos Aires, 60
importance of breast feeding, 402
incidence and mortality of breast and artificially fed infants admitted to hospital with infections, 225
influence of diet on physiologic anemia of infants, 71
medical, social and economic study of feeding of well infants in organization for protection of maternal welfare in Chile, 59
milk problem in Chile, 226
relation of maternal diet to breast feeding, 225
use of evaporated milk without added sugar for, *52
use of "Leitelho" as therapeutic and prophylactic food in child health centers, 144
vitamins and artificial feeding, 60
Infant Mortality: See also Newborn Infants; Premature Infants
causes of fetal and neonatal death, 404
certification of death in infancy, 62
in Rio de Janeiro, Brazil, 316
in rural and urban areas, 61
question of mortality in infants and children in India, laying special emphasis on measures to control it, 316
Infant Welfare: See also Child Welfare
economic and social aspects of artificial feeding in program of infant welfare protection in Buenos Aires, 60
medical, social and economic study of feeding of well infants in organization for protection of maternal welfare in Chile, 59
Infantile Paralysis: See Poliomyelitis
Infantilism, Intestinal: See Celiac Disease
Renal: See Dwarfism
Infants: See also Children; Infant Feeding; Infant Mortality; Infant Welfare; Newborn Infants; Pediatrics; Premature Infants; etc.
Diseases: See under names of various diseases
Growth: See Growth
psychogenic fever in, *176
speech sound elements during first year of life; review of literature, 413
Infarction: See under Kidneys
Infection: See also Immunity; and under names of bacteria, organs and regions, as Staphylococci; etc.
mode of action of gramicidin and penicillin in treatment of infections, 320
Infectious Diseases: See Communicable Diseases; Diphtheria; Infection; Pneumococci; Typhoid; etc.
Influenza, epidemic in military camp in Victoria, May 1942, 232
experimental immunization of volunteers against influenza virus B, 409
Hemophilus influenzae meningitis in infant treated with sulfathiazole, 237
influenzal meningitis, *194
intranasal vaccination of humans with living attenuated influenza virus strains, 409
virus pneumonias; pneumonias associated with known nonbacterial agents; influenza, psittacosis and Q fever, 150
Infra-Red Rays: See Neuritis; Poliomyelitis
Injections: See Blood, transfusion; Insulin; etc.
Injuries: See under Newborn Infants; and under names of organs and regions, as Head; etc.
Insensible Perspiration: See Metabolism
Insulin: See also Diabetes Mellitus; Pancreas
initial stabilization of diabetic child, *429
Intelligence Tests: See Mental Tests
Intertrigo, persistent; diagnosis, 239
Intervertebral Disks: See under Spine
Intestines: See also Colon; Duodenum; Gastrointestinal Tract; Rectum; Sigmoid
abnormalities; congenital anomalies of primary midgut loop, 74
acute intestinal infection with no specific lesions of, 152
Diseases: See also Diarrhea; Dysentery; etc.

Intestines—Continued
diseases; infection and therapy with sulfonamide compounds in cases of gastrointestinal disorders and enteritis of infancy, 77
infection and sulfonamide therapy in digestive disturbances and enteritis of infancy, 152
infectious diseases with specific lesions of intestinal tract, 152
Intussusception: See Intussusception
mode of laxative action of phenolphthalein, 73
Parasites: See Amebiasis; Dysentery; Lambliasis; Tapeworm Infection
Staphylococcus aureus in milk of nursing mothers and alimentary canal of their infants, 225
sulfonamide therapy in nutritional disturbances, 144
vitamin A absorption and its relation to intestinal motility in fibrocystic disease of pancreas, 76
Intussusception, 152
intestinal invagination in infancy, 497
Inulin: See Kidneys, function tests
Iodine and Iodine Compounds, effect of chloride with high and low iodine supply on thyroid gland of rat, 419
Iris, anomalous processes of ciliary type on posterior surface of, 157
displacement of ciliary processes to posterior surface of, 157
Islands of Langerhans: See Pancreas
Ivy Poisoning: See Rhus, poisoning

Jackson, R. L.: Comparison of Westergren and Kato erythrocyte sedimentation rate readings; relation to clinical status of children with rheumatic fever, *474
Jaundice: See also Erythroblastosis, Fetal
icterus gravis neonatorum, 87
Jaws, osteomyelitis of superior maxilla in infant, 157
Jejunum: See Intestines
Johnston, J. A.: Factors influencing retention of nitrogen and calcium in period of growth; calcium and vitamin D requirements of older child, *265
Joints: See also under names of individual joints, as Hip; etc.
ankylosis; arthrogryposis multiplex congenita, 498
Diseases: See Arthritis; etc.
Jones, C. P.: Ascorbic acid, riboflavin and thiamine content of cow's milk; influence of ration, *376
Josephs, H. W.: Hypervitaminosis A and carotenemia, *33

Kahn Test: See also Syphilis
Kahn verification test in malaria (differential diagnosis of syphilis), 408
Kato Method: See Blood, sedimentation
Katsampes, C. P.: Vitamin A absorption test in cases of giardiasis, *189
Kenny Method: See Poliomyelitis
Keratin, experimental eosinophilia with keratin from Ascaris suum and other sources, 65
Keratitis, Nodular: See Cornea
Keratoconjunctivitis, phlyctenular, Bouquet-Nègre antigen and its use in treatment of, 158
Kernicterus: See under Jaundice
Ketosis: See Acidosis
Ketosteroids: See Urine, steroids
Kidneys: See also Urinary Tract
acute nephritis and effect of sulfonamides on, 417
Carbuncle: See Nephritis
Diseases: See also under Nephritis
diseases; amino acid studies; plasma amino acid retention, as evidence of impaired liver function; investigations in children with nephrosis and liver disease, 400
disturbed kidney function in newborn infant associated with decreased calcium: phosphorus ratio, 404
fatal anuria following administration of sulfonamides with reference to tubular necrosis and regeneration, 417
Function Tests: See also Diuresis and Diuretics; Urea, clearance
function tests; diodrast and inulin clearances in nephrotic children with supernormal urea clearances, 417
infarct, 238
renal function with new nomographic method for determination of urea clearance, 329
Kidneys—Continued
secretion of urine by dehydrated and normal infants, 154
severe injury to kidneys and brain following sulfathiazole administration; high serum sodium and chloride levels and persistent cerebral damage, 500
toxicity and pharmacology of riboflavin, 61
Kinesthesia, comparison of kinesthetic sensibility to speech-defective and normal-speaking children, 80
Klasmer, R.: Serum phosphatase activity and clinical rickets in children in Jerusalem, *348
Knee: See Patella
Koch's Bacillus: See Tubercle Bacilli
Kochia Scoparia: See Hay Fever
Kohn, J. L.: Roentgenograms of chest taken during pertussis, *463
Kohn, P. M.: Poliomyelitis; results of treatment during acute stages of disease, *393
Koilonychia: See Nails
Kriete, F. A.: Levinson ratio and tryptophan test; comparative value in diagnosis of tuberculous meningitis, *469

Labor: See also Obstetrics; Pregnancy; etc.
fetal distress during labor, 403
hemangioma of arm causing delay in delivery and neonatal death, 404
Lactation: See also Colostrum; Infant Feeding; Milk
effectiveness of linoleic, arachidonic and linolenic acids in reproduction and lactation, 58
failing, 225
mechanism controlling initiation at parturition, 57
reflex governing outflow of milk from breast, 226
relation of maternal diet to breast feeding 225
Lactobacillus: See Bacteria, lactic acid group
Lactogen: See Pituitary Body
Lages Netto, D. J.: Ganglioneuroma of breast in 5 year old child, *382
Pneumopericardium in 42 day old infant, *288
Lambliasis, vitamin A absorption test in cases of giardiasis, *189
Langerhans' Islands: See under Pancreas
Lapin, J. H.: Recurrent and chronic diarrhea in infancy and childhood, *139
Larkin, V. deP.: Relapsing febrile nodular nonsuppurative panniculitis (Weber-Christian disease); review of literature, with report of case, *120
Laryngotracheobronchitis: See Respiratory Tract, diseases
Laryngitis: See under Larynx
Larynx, laryngitis, 150
Lattimer, J. K.: Similar urogenital anomalies in identical twins, *199
Laurence-Moon-Biedl Syndrome, report of 2 cases with unusual combinations of heredofamilial deviations, 83
Laxatives: See Phenolphthalein and Phenolphthalein Derivatives
Lead, studies in deposition of lead in bone; calcification and lead deposition, 499
toxicity; effect of sodium citrate administration on excretion of lead in urine and feces, 331
Lecithin: See Lipoids
Lederer's Anemia: See Anemia, hemolytic
Lederle's Pertussis Antigen: See Whooping Cough
Legg-Perthes Disease: See Osteochondritis deformans juvenilis
Legislation, law in behalf of social defense for children, 490
Leitelho: See Infant Feeding
Lens, Crystalline; arachnodactyly in 4 siblings with pneumoencephalographic observations of 2, *201
arachnodactyly (Marfan's syndrome), 144
fibroblastic overgrowth of persistent tunica vasculosa lentis in infants born prematurely, 238
Leprosy, antiquity of congenital syphilis (described as leprosy), 145
experimental, effect of sulfanilamide on, 322
Leptomeningitis: See Choriomeningitis
Leukemia, lymphatic, unusual manifestation of, 234
Leukocytes: See also under Blood; Eosinophils; Leukemia; etc.
enumeration and differentiation in counting chamber with propylene glycol-aqueous stains, 324
Leukopenia: See Hemoclastic Crises
Levinson, S. O.: Special aspects of poliomyelitis in 1943, 332

Levinson Ratio: See Cerebrospinal Fluid
Limbs: See Arms
Lipemia: See Blood, fats and lipoids
Lipid Pneumonia: See Pneumonia
Lipids: See Blood, fats and lipoids; Lipoids
Lipoidosis: See Idiocy; Lipoids
Lipoids: See also Fat
acrolein and shock; possible relationship of lipoid breakdown products to shock associated with burns, 499
in Blood: See Blood, fats and lipoids
influence of lecithin feeding on fat and vitamin A absorption in man, 401
Pneumonia: See Pneumonia
Little's Disease: See Paralysis, spastic
Litvak, A. M.: Pneumococcic meningitis; complete recovery of 6 month old infant treated with penicillin, *485
Liver, amino acid studies; plasma amino acid retention, as evidence of impaired liver function; investigations in children with nephrosis and liver disease, 400
extract in arsenical intolerance, 240
Glycogen: See Glycogen
large solitary bile-cell fibroadenoma of, 76
plasma prothrombin and liver function during sulfonamide therapy, 86
solitary nonparasitic cyst of, 74
Therapy: See Anemia
Loeffler's Bacillus: See Diphtheria
Lues: See Syphilis
Lumbar Puncture: See Spinal Puncture
Lumbosacral Region: See Backache; Spine
Lungs: See also Bronchi; Pleura; Respiration; Respiratory Tract; Thorax; etc.
acute putrid abscess; criteria of cure, 71
calcification, and tuberculin sensitivity among children in Williamson County, Tennessee, 410
collapse; atelectasis complicating acute poliomyelitis with involvement of respiratory muscles, *457
collapse; bronchial obstruction and pulmonary atelectasis, 233
collapse; obstructive emphysema and atelectasis in tuberculosis of infants and children, 323
Diseases: See also Tuberculosis, pulmonary; etc.
diseases, chronic, in childhood, 414
diseases; prevention of chronic lung diseases in childhood, 73
edema; fatal case of tachycardia in infant, 234
pneumatocele, or localized bullous emphysema following pneumonia, 414
pulmonary hemosiderosis in 6 year old boy; clinical and pathologic report, *387
Tuberculosis: See Tuberculosis, pulmonary
Lymph Nodes: See also Leukemia, lymphatic; etc.
cervical adenitis, 150
roentgenograms of chest taken during pertussis, *463
Lymphatic System: See Lymph Nodes
Lymphocytes: See Leukemia; Leukocytes
in Meningitis: See Choriomeningitis
Lymphoid Tissues: See Adenoids; Tonsils; etc.
Lysine deficiency, biochemical lesion in man, 314
Lyttle, John D., new appointment for, 335

McCoord, A. B.: Vitamin A absorption test in cases of giardiasis, *189
McCulloch, H.: Use of evaporated milk without added sugar for feeding infants, *52
McCune, D. J.: Mental development of congenitally hypothyroid children; its relationship to physical development and adequacy of treatment, *205
McKinley, J. B.: Comparison of Westergren and Kato erythrocyte sedimentation rate readings; relation to clinical status of children with rheumatic fever, *474
Macklin, M. T.: Erythroblastosis fetalis; proposed definition and clarification of term, *445
Macrogenitosomia: See Puberty
Madonick, M. J.: Arachnodactyly in 4 siblings with pneumoencephalographic observations of 2, *201
Magnesium, deficiency, tetany due to; its occurrence in child of 6 years with associated osteochondrosis of capital epiphysis of femur (Legg-Perthes disease), *117
Malaria, cerebellar syndrome of malarial origin, 233
Kahn verification test in malaria (differential diagnosis of syphilis), 408
Malaria—Continued
subtertian, place of quinine in treatment of, 322
Therapeutic: See under Poliomyelitis
views on origin in 1843, 409
Malformations: See Monsters; and under names of organs and regions
Malnutrition: See under Dystrophy; Nutrition
Mammary Gland: See Breast
Mandible: See Jaws
Mantoux Reaction: See Tuberculosis
Marchiafava-Micheli Syndrome: See Anemia, hemolytic; Hemoglobinuria
Marfan Syndrome: See Arachnodactylia
Margulis, A. E.: Relapsing febrile nodular nonsuppurative panniculitis (Weber-Christian disease); review of literature, with report of case, *120
Marks, H. H.: Prophylaxis of measles with convalescent serum; principal factors influencing results, *1
Masks, initial aerobic flora of newborn (premature) infants; nature, source and relation to ultraviolet irradiation and face masks, *89
Mason, A. S., Jr.: Prophylactic value of sulfathiazole against neonatal gonococcic conjunctivitis, *472
Mastoid, Inflammation: See Mastoiditis
surgery; sulfathiazole in mastoidectomy wounds, 326
Mastoiditis: See also Otitis Media
silent, 235
Maté (Ilex paraguayensis), innovation in fluid diet in infancy, 226
Maternity: See also Labor; Obstetrics; Pregnancy
antepartum examination, 159
Maternity Welfare, effect of war on program in Illinois, 315
Maxilla: See Jaws
Mazzini Test: See Syphilis
Measles, attack rate and incubation period; significance of age and of conditions of exposure, *15
course in diabetes mellitus of childhood, 148
influence of social conditions on diphtheria, measles, tuberculosis and whooping cough in early childhood in London, 232
myocarditis in, *298
prophylaxis of measles with convalescent serum; principal factors influencing results, *1
results following inoculation of children with egg-passage measles virus, 317
results of chance and planned exposure to unmodified measles virus in children previously inoculated with egg-passage measles virus, 318
sulfathiazole in treatment of measles and its complications, 63
Mebaral: See Epilepsy
Medicine, Military: See Military Medicine
Medin-Heine Disease: See Poliomyelitis
Mediterranean Anemia: See Anemia, erythroblastic
Meiselas, L. E.: Bleeding peptic ulcer in infancy, *384
Memory, importance of sensory training in speech therapy, 154
Menarche: See Menstruation
Meninges: See also Arachnoid
hemorrhage, extradural, 153
hemorrhage; fatal intracranial venous hematoma following ventricular drainage, 153
tuberculosis; hemiplegia in tuberculous meningitis, 233
tuberculosis; Levinson ratio and tryptophan test; comparative value in diagnosis of tuberculous meningitis, *469
Meningitis: See also Choriomeningitis; Meningococci
cerebrospinal fever treated by chemotherapy; review of 500 cases treated by chemotherapy without intrathecal serum, 64
diagnosis and management of severe infections in infants and children; review of experiences since introduction of sulfonamide therapy; hemolytic streptococcic meningitis, 66
epidemic cerebrospinal meningitis with recurrence, 147
epidemic, myocarditis in, *299
epidemic, relation of carrier to, 405
Hemophilus influenzae meningitis in infant treated with sulfathiazole, 237
hypertrophic cervical meningitis of tuberculous origin, 148

Meningitis—Continued
influenzal, *194
pneumococcic; complete recovery of 6 month old infant treated with penicillin, *485
pneumococcic, treated with sulfathiazole, 153
prophylaxis and treatment of epidemic cerebral meningitis, 231
streptococcic, in nursing baby, with recovery, 154
treatment of cerebrospinal fever by sulfapyridine, 230
Tuberculous: See Meninges, tuberculosis
tularemic; report of case and summary of previously reported cases, *44
Meningococci: See also Meningitis
meningococcosis of locomotor apparatus, 319
skin manifestations of meningococcal infection, 230
Meningoencephalitis: See Encephalitis; Meningitis
Menstruation, menarche in relation to climate, 155
menarcheal age and height, weight and skeletal age of girls age 7 to 17, 489
Mental Diseases: See Nervous and Mental Disabilities; Neuroses and Psychoneuroses; Psychiatry; etc.
Mental Tests: See also Personality
intelligence tests for deaf-mutes, 327
mental development of congenitally hypothyroid children; its relationship to physical development and adequacy of treatment, *205
Menten, M. L.: Cystic fibrosis of pancreas; report of 18 proved cases, *355
Mercury, sulfanilamide bacteriostasis in presence of mercuric chloride and *p*-aminobenzoic acid, 501
Mester Test: See Hemoclastic Crisis
Metabolism: See also under specific headings, as Carbohydrates; Nitrogen; Sulfur; Water; etc.
cardiovascular and metabolic study of stutterers and non-stutterers, 413
effect of glucose and sucrose on respiratory quotient and muscular efficiency of exercise, 58
interrelationship of calcium, phosphorus and nitrogen in metabolism of preschool children, 58
Meteorology: See also Climate
clinical episode in tuberculosis and meteorologic environment, 69
Methionine, inhibiting effect of methionine, choline and betaine on rabbit's susceptibility to infection with vaccinia, 67
nitrogen balance in experimental human deficiencies of methionine and cystine, 314
Methylene-Bis-(Hydroxycoumarin): See Coumarin
Methylethylphenobarbital: See Epilepsy
Mexico, smallpox epidemic of 1797 in, 145
Microscopy, Electron: See Bacteria
Micturition: See Urination
Middleton, T. O.: Cystic fibrosis of pancreas; report of 18 proved cases, *355
Midget: See Dwarfism
Military Medicine: See also Aviation and Aviators
bacillary dysentery caused by Bacterium dysenteriae P274, 409
bacillary dysentery; some results and conclusions from series of patients treated with sulfaguanidine, 409
influenza epidemic in military camp in Victoria, May 1942, 232
official statistics on speech disorders encountered during World War I, 413
Schick reactions and diphtheria immunization of South African Field Hospital Staff in Middle East, 407
tetanus toxoid; its use in United States Army, 493
Milk: See also Colostrum; Infant Feeding
ascorbic acid, riboflavin and thiamine content of cow's milk; influence of ration, *376
cleansing and sterilization of milk bottles, 401
comparative nutritive value of butter fat and vegetable oils, 488
Human: See also Infant Feeding; Lactation
human; presence of Rh antibodies in breast milk; further investigations, 401
human, probable idiosyncrasy to, 158
human, secretion of radioactive sodium in, 314
milk-borne outbreak of gastroenteritis in Oklahoma City, 77
milk-borne outbreaks due to serologically hemolytic streptococci, 493
policy for children, 402
problem in Chile, 226
Milk—Continued
series of substitutes in treatment of allergies, 85
sore throat outbreak in upstate hospital, 412
Staphylococcus aureus in milk of nursing mothers and alimentary canal of their infants, 225
use of evaporated milk without added sugar for feeding of infants, *52
Miller, J. F.: Tetany due to deficiency in magnesium; its occurrence in child of 6 years with associated osteochondrosis of capital epiphysis of femur (Legg-Perthes disease), *117
Mines and Miners, problem of hypermetropic miner, 330
Minot, A. S.: Serum tocopherol; its relation to failure of vitamin E therapy for pseudohypertrophic muscular dystrophy, *371
Mirsky, I. A.: Ketosis in relation to hepatic reserves of glycogen; study of normal and of diabetic children, *100
Moles: See Nevi
Molluscum contagiosum of eye, 499
Mongolism, persistent common atrioventricular ostium in child with mongolism, 149
Moniliasis, oral, in newborn infants, *450
Monsters, cephalic; hydranencephaly; report of 2 cases which combine features of hydrocephalus and anencephaly, *282
Moon-Laurence-Biedl Syndrome: See Laurence-Moon-Biedl Syndrome
Morbus Cushing: See under Pituitary Body
Morphine, effect on electrical activity of cortex of certain depressant and stimulant drugs; barbiturates, morphine, caffeine, benzedrine and adrenalin, 497
Mortality Statistics: See Infant Mortality; Newborn Infants; etc.
Mosquitoes: See Encephalitis
Mouth: See also Stomatitis
oral moniliasis in newborn infants, *450
Riga-Fede disease, 152
Movements, Fetal: See Fetus
misarticulation and diadokokinesis in spastic paralytic, 497
Mucous Membrane: See Mouth; Nose; Stomach; etc.
Münchmayer's Disease: See Myositis ossificans
Mumps: See Parotitis
Muschat, M.: Occlusion of urethral meatus, *275
Muscles, abnormalities; arthrogryposis multiplex congenita, 498
Dystrophy: See Dystrophy, muscular
Glycogen: See Glycogen
Ossification: See Myositis ossificans
Paralysis: See Paralysis
subclinical vitamin deficiency; thiamine in skeletal muscle of infants and children, *30
Tonus: See Myatonia
Myatonia congenita; amyotonia (myatonia) congenita; Oppenheim's disease, 156
Mycosis: See also Actinomycosis; Ringworm; etc.
mycotic endocarditis; report of case with necropsy; review of literature, *128
Myelitis: See Encephalomyelitis
Myelosis: See Bones, marrow
Myocarditis associated with endocarditis, *304
fetal, *296
in children, *294
in contagious and infectious diseases, *296
in tuberculosis, *307
isolated, *301
rheumatic, *306
Myocardium: See Heart; Myocarditis
Myopathy: See under Muscles
Myositis: See also Dermatomyositis
ossificans, multiple progressive; disease of Münchmayer, 156
Myxedema: See Thyroid, hypothyroidism
Congenital: See Cretinism
Myxoma, effect of temperature on growth and survival of myxoma, herpes and vaccinia viruses in tissue culture, 56

Nails, hypochromic anemia with koilonychia (spoon nails), 149
Nanism: See Dwarfism
Naphthoquinone: See Vitamins, K
Neck, Lymph Nodes: See Lymph Nodes
Necrosis: See Pancreatitis

Nègre-Bouquet Antigen: See Keratoconjunctivitis
Neisseria: See Bacteria, neisseria
Nelson, W. E.: Ketosis in relation to hepatic reserves of glycogen; study of normal and of diabetic children, *100
Nematodes: See Oxyuriasis; etc.
Neoarsphenamine: See Syphilis
Neoplasms: See Cancer; etc.
Nephritis: See also Kidneys, diseases
acute, and effect of sulfonamides on kidneys, 417
acute, and tonsillectomy, 82
chronic, physiology of, 418
electrocardiographic variations in acute glomerulonephritis, *106
glomerulonephritis; some cases treated with sulfanilamide, 155
Nephrosis: See Kidneys, diseases; Nephritis
Nerves: See also Nervous System; Neuritis; Paralysis
earache; common causes and probable nerve pathways, 326
effect of bone dysplasia on cranial nerves in vitamin A deficient animals, 315
optic; nutritional degeneration of optic nerve in rats; its relation to tryparsamide amblyopia, 238
peripheral, local application of sulfanilamide to, 240
Nervous and Mental Disabilities: See also Encephalitis; Idiocy; etc.
study of emotions and mental states in infants, 154
Nervous System: See also Brain; Cerebellum; Nerves; Reflex; Spinal Cord; etc.
autonomic nervous system function in children with behavior problems as measured by parotid secretory rate, 237
Diseases: See Epilepsy; Mental Diseases; Neuritis; Neuroses and Psychoneuroses; etc.
Syphilis: See Neurosyphilis
Tumors: See Ganglioneuroma; etc.
use of vitamins in clinical neurology, 227
Neuritis, effect of infra-red heat on localized poliomyelitis and neuritis, 329
polyneuritis in patient with whooping cough, 148
Neurohypophysis: See Pituitary Body
Neuroses and Psychoneuroses: See also Mental Diseases; Nervous and Mental Disabilities
prognostic factors of adolescent psychoses, 81
Neurosyphilis, fever therapy, 501
Neurotropism: See Streptococci
Neutrophils: See Leukocytes
Nevi, flammeus treated by thorium X, 239
moles and malformations of skin, 158
symmetric, of face, tuberous sclerosis, epilepsy and fibromatous growth on scalp, with abnormal electroencephalograms of members of family, 330
Vascular: See Angioma
Newborn Infants: See also under names of diseases, as Anemia; Asphyxia; Conjunctivitis; Cyanosis; Jaundice; Meningitis; Syphilis; etc.
acute scleroma, 404
asphyxia and its treatment, 144
blood sugar in, 228
carbonic anhydrase (in relation to cyanosis and blood transfusion), 404
colon in healthy newborn infant, 77
dactyloscopy in identification of, 229
disorders of, 317
encephalitis following inclusion conjunctivitis, 228
hemorrhagic disease of, 228
occurrence of abnormal capillary fragility in, 403
oral moniliasis in, *450
pneumopericardium in 42 day old infant, *288
prophylactic value of sulfathiazole against neonatal gonococcic conjunctivitis, *472
respiratory disturbances in, 403
role of colon organisms and their toxins in epidemic diarrhea of, 228
study of humoral antibodies for Staphylococcus aureus in infants and their mothers, 408
sulfaguanidine in neonatal epidemic gastroenteritis, 414
vitamin K in hemorrhagic disease of, 228
vitamin K requirements of, 228
Nicotinic Acid: See also Vitamins, B
content of common fruits and vegetables as prepared for human consumption, 315
evaluation of nicotinic acid nutrition by studies of urinary excretion, 61
in foods, 61
treatment of stomatitis aphthosa; 3 cases, 152
Nipple: See Breast
Nippostrongylus Muris: See Trichostrongylidae
Nitrogen, biochemical lesion of lysine deficiency in man, 314
factors influencing retention of nitrogen and calcium in period of growth; calcium and vitamin D requirements of older child, *265
interrelationship of calcium, phosphorus and nitrogen in metabolism of preschool children, 58
metabolism; calcium, phosphorus and nitrogen metabolism of young college women, 59
metabolism; nitrogen balance in experimental human deficiencies of methionine and cystine, 314
storage following intravenous and oral administration of casein hydrolysate to infants with acute gastrointestinal disturbance, 400
sulfur metabolism of children, 58
Nodes: See Lymph Nodes; Rheumatic Fever
Nomenclature, epitome of agnosia, apraxia and aphasia with proposed physiologic-anatomic nomenclature, 154
erythroblastosis fetalis; proposed definition and clarification of term, *445
Nomogram: See Urea
Nose: See also Otorhinolaryngology; Rhinitis; etc.
sinusitis and nasal allergy, 150
treatment of congenital atresia of choanae, 234
Nutrition: See also Diet and Dietetics; Dystrophy; Food; Infant Feeding; Metabolism; Vitamins; etc.
infection and therapy with sulfonamide compounds in cases of gastrointestinal disorder and enteritis of infancy, 77
nutritional anemia in children and women; wartime problem, 325
nutritional needs of American youth, 488
nutritive adequacy of certain low-cost food mixtures, 401
slit lamp microscope in nutrition surveys, 227
sulfonamide therapy in nutritional disturbances, 144
surveys of nutrition of populations; part 2, 487
Nycturia: See Urination, incontinence

Obesity: See also Laurence-Moon-Biedl Syndrome; Pituitary Body
new trends in treatment; role of physical medicine, 225
OBITUARIES:
Carr, Walter Lester, 241
Hempelmann, Theodore Carl, 241
Obstetric Injuries: See under Newborn Infants
Obstetrics: See also Hospitals; Labor; Maternity; Pregnancy; etc.
Rh factor and its application to obstetric practice, 405
Occupations: See Industry
Odors, allergy to food odors; its relation to management of infantile eczema, 421
Oil, comparative nutritive value of butter fat and vegetable oils, 488
Oligodendroglioma in infant of 8 months, 498
Ombredanne's Syndrome: See Shock
Omphalocele: See Hernia, umbilical
Oppenheim's Disease: See Myatonia congenita
Optic Chiasm, optochiasmic arachnoiditis, 415
Optic Disk: See Nerves, optic
Oranges, relation of season, weight and price to vitamin C content of, 489
Orchitis: See Testes
Orthodontia: See Dentistry; Teeth
Orthodontics: See Jaws
Orthopedics: See also Poliomyelitis
role of orthopedic appliances in treatment of infantile paralysis, 230
Osmyls: See Odors
Ossification: See Bones, growth; Lungs; etc.

Osteochondritis deformans juvenilis; tetany due to deficiency in magnesium; its occurrence in child of 6 years with associated osteochondrosis of capital epiphysis of femur (Legg-Perthes disease), *117
Osteogenesis: See Bones, growth
Osteomyelitis of superior maxilla in infant, 157
Otalgia: See Earache
Otitis Media, 150. See also Mastoiditis
acute, sulfonamide drugs in treatment, 325
Otorhinolaryngology, principles of diagnosis and treatment of allergy as related to otolaryngology, 422
vitamin therapy today, 227
Otorrhea: See Ear, discharge
Ovary, adrenocortical-like tissue in ovaries of adrenalectomized ground squirrel (Citellus tridecemlineatus), 419
Owens, J. N., Jr.: Tularemic meningitis; report of case and summary of previously reported cases, *44
Oxygen: See also Respiration
deficiency; fetal distress during labor, 403
in Blood: See Blood, oxygen
Oxyuriasis; enterobiasis in children, 66
examination of 1,551 Mexican children by Graham method, 494

Palsy: See Paralysis
Pancreas, blood amylase activity in disease of carbohydrate metabolism and in nondiabetic pancreatic disease, 411
cystic fibrosis; report of 18 proved cases, *355
Necrosis: See Pancreatitis
vitamin A absorption and its relation to intestinal motility in fibrocystic disease of, 76
Pancreatitis, necrosis of islets of Langerhans produced experimentally (by styrl quinoline and alloxan), 415
Panmyelophthisis: See Anemia
Panniculitis, relapsing febrile nodular nonsuppurative panniculitis (Weber-Christian disease); review of literature, with report of case, *120
Pantothenate: See Vitamins, B
Pantothenic Acid: See Vitamins, B
Pantoyltaurine, chemotherapy by blocking bacterial nutrients; antistreptococcal activity of pantoyltaurine, 400
Paraffin, concentrations of sulfadiazine in human saliva attained by chewing paraffin containing sulfadiazine, 240
Paralysis: See also Eyes, paralysis; Hemiplegia; Poliomyelitis; etc.
atelectasis complicating acute poliomyelitis with involvement of respiratory muscles, *457
Bell's: See Paralysis, facial
Bulbar: See Poliomyelitis
facial; congenital paralysis of lateral rotators of eyes with paralysis of muscles of face, 416
Infantile: See Poliomyelitis
pathology of cerebral diplegia, 79
Respiratory: See under Respiration
spastic; misarticulation and diadokokinesis in spastic paralytic, 497
spastic situation, 497
spastic; treatment of spastic diplegia or Little's disease, 154
transient, due to bite of American dog tick (Dermacentor variabilis Say), *126
Parasites: See also under names of parasitic diseases, as Oxyuriasis; etc.
threadworms, 87
Parathyroid, experiments on dental lesions of glandular origin, 156
relationship of low blood calcium to parathyroid secretion, 83
Parotid Gland, autonomic nervous system function in children with behavior problems as measured by parotid secretory rate, 237
Parotitis, experimental mumps; transmission of disease to monkeys; attempts to propagate virus in developing hen's eggs, 493
immunity in mumps, 405
mumps with edema of chest, 317
myocarditis in, *298
surgical treatment of severe orchitis in mumps, 147
Parturition: See Labor
Pasachoff, H. D.: Arachnodactyly in 4 siblings with pneumoencephalographic observations of 2, *201
Pasteurella: See Bacteria, pasteurella
Patch Test: See Anaphylaxis and Allergy; Tuberculosis
Patella, vibration of thorax by percussion of skull and patella, 159
Peaches, influence of variety, size and degree of ripeness on ascorbic acid content of peaches, 489
Pediatric societies, directory of, 162, 242, 336, 424, 506
Pediatrics: See also Children; Hospitals; Newborn Infants; and under names of specific diseases
importance of orthodontia in, 159
psychiatrist and behavior problem, 329
Pellagra: See also Riboflavin
control of, 227
Pellizzi Syndrome: See Puberty
Pelvis: See also Genitourinary Tract
antepartum examination, 159
Penicillin, absorption, excretion and distribution of, 501
chemotherapeutic effect of esters of, 502
general and local administration of, 502
mode of action of gramicidin and penicillin in treatment of infections, 320
Therapy: See Meningitis
toxicity and efficacy of, 240
Peptic Ulcer, bleeding, in infancy, *384
chronic gastric ulcer in 6 year old child, 74
Percussion, vibration of thorax by percussion of skull and patella, 159
Pericarditis, Rheumatic: See Rheumatic Fever
Perlstein, M. A.: Fatal effects of prolonged complete curarization, *360
Personality, irresponsibility of juvenile delinquents, 237
Perspiration, Insensible: See Metabolism
Perthes' Disease: See Osteochondritis deformans juvenilis
Pertussis: See Whooping Cough
Peshkin, M. M.: Immunity to tetanus induced by third dose of toxoid 3 years after basic immunization, based on study of 38 allergic children, *22
Pfeiffer's Bacillus: See Influenza
Phagocytes and Phagocytosis: See Immunity; Leukocytes
Phenolphthalein and Phenolphthalein Derivatives, mode of laxative action of phenolphthalein, 73
Phillips, W. A.: Vitamin A absorption test in cases of giardiasis, *189
Phimosis in infancy, 418
Phonation: See Speech
Phosphatase in Blood: See under Blood
Phosphate: See Phosphorus and Phosphorus Compounds
Phosphorus and Phosphorus Compounds, calcium, phosphorus and nitrogen metabolism of young college women, 59
effect of dietary fat on bone calcification in growing rat, 488
in Blood: See Blood, phosphorus
interrelationship of calcium, phosphorus and nitrogen in metabolism of preschool children, 58
tubular reabsorption of phosphate in dog, 400
vitellin, casein, liver and muscle tissue as sources of phosphorus for rachitic rat, 402
Physical Therapy: See also Ultraviolet Rays; under names of diseases, organs and regions; etc.
new trends in treatment of obesity; role of physical medicine, 225
Physicians: See Obituaries
Pilcher, J. D.: Pulmonary hemosiderosis in 6 year old boy; clinical and pathologic report, *387
Pink Disease: See Acrodynia
Pinworms: See Oxyuriasis
Pitressin: See Pituitary Preparations
Pituitary Body, Diseases: See also Laurence-Moon-Biedl Syndrome; Obesity; etc.
diseases; electrocardiogram of Cushing's syndrome, 155
effects of hormones on erythropoieses in hypophysectomized rat, 83
hypophysial dwarfing, 156

Pituitary Body—Continued
mechanism controlling initiation of lactation at parturition, 57
role of anterior pituitary in adrenalin hyperglycemia and liver glycogenolysis, 82
Pituitary Preparations, antagonism of pitressin and adrenal cortical extract in human diabetes insipidus, 83
relation of mammogenic lobule-alveolar growth factor of anterior pituitary to other anterior pituitary hormones, 155
Plague, sylvatic plague studies; fate of Pasteurella pestis in flea, 313
Plants, Poisonous: See Rhus
Pleura, tuberculosis; effect of pleural effusions on growth of Staphylococcus aureus in vitro, 313
Plumbism: See Lead, toxicity
Pneumococci, Infections: See under Meningitis; Pneumonia
pneumococcic septicemia ending with Henoch's purpura (idiopathic nonthrombopenic purpura), 148
reversibility of quellung reaction and relation between quellung reaction and bile solubility, 56
studies on sulfonamide resistant organisms; origin of sulfonamide-resistant pneumococci, 331
Pneumoencephalography: See under Brain
Pneumonia: See also Bronchopneumonia
atypical, identification of 2 strains of virus isolated from cases of, 72
clinical and bacteriologic survey in childhood, 496
consideration of respiratory pattern as predisposing factor in etiology of, 72
lipid, 327
lobar, sulfadiazine in treatment, 235
myocarditis in, *300
pneumatocele, or localized bullous emphysema following pneumonia, 414
similarity of cytoplasmic inclusions in infant pneumonitis and bovine epithelial cells, 72
sulfadiazine, 159
Tuberculosis: See Tuberculosis, pulmonary
virus pneumonia, 235
virus pneumonias; pneumonias associated with known nonbacterial agents: influenza, psittacosis and Q fever, 150
Pneumonitis: See Pneumonia
Pneumopericardium in 42 day old infant, *288
Pneumothorax: See Tuberculosis
Poison Ivy: See Rhus, poisoning
Poisons and Poisoning: See under names of substances, as Curare; Lead; etc.
Poliomyelitis: See also Encephalomyelitis
acute anterior, 319
and tonsillectomy; new concept of etiologic relationship, 406
anterior, Kenny versus orthodox treatment of, 492
anterior, nonspecific therapy; preliminary report on use of vitamins B and E and artificial fever, 318
anterior, surgical treatment of, 319
atelectasis complicating acute poliomyelitis with involvement of respiratory muscles, *457
attempts to propagate virus of poliomyelitis in smaller laboratory animals, 405
atypical, 333
clinical aspects, 332
differential diagnosis, 334
early treatment of, 63
effect of infra-red heat on localized poliomyelitis and neuritis, 329
epidemic, community study of carriers in, 317
epidemiologic and experimental observations on possible significance of rodents in suburban epidemic, 491
hypothetical relationship of water supplies to, 491
in United States in 1942, and summary of its prevalence from 1933 to 1942 inclusive, 406
infantile paralysis, 230
Kenny method in treatment of acute and subacute poliomyelitis, 320
Kenny treatment of, 492
mechanism of Kenny method and its correlation with vitamin B therapy, 229
modern views of etiology and early diagnosis, 406
Poliomyelitis—Continued
myocarditis in, *299
nonparalytic forms of Heine-Medin disease (acute anterior poliomyelitis), 407
orthopedic treatment of infantile paralysis, 319
pathologic changes in, 333
relationship between benign lymphocytic meningitis and poliomyelitis, 320
results of treatment during acute stages of disease, *393
role of orthopedic appliances in treatment of infantile paralysis, 230
special aspects in 1943, 332
thiamine excretion tests in children with paralytic poliomyelitis, 318
treatment of infantile paralysis during period of restoration and orthopedic prophylaxis, 147
types of deformities following infantile paralysis as observed in Hospital Arriaran, 147
Pollen: See Anaphylaxis and Allergy; Asthma; Hay Fever
Polyneuritis: See Acrodynia; Neuritis
Polysaccharide: See Blood, sugar
Polyuria: See Diabetes Insipidus
Pontocaine: See Anesthesia
Potassium, comparison of sodium and potassium metabolism of asthmatic and nonallergic children, 421
Pregnancy: See also Fetus; Labor; Maternity; Obstetrics
colostrum as source of diphtheria antitoxin in actively immunized pregnant mothers, 318
Multiple: See Twins
urine in; excretion of ketosteroids in human pregnancy urine in relation to sex of fetus, 403
Premature Infants, care of, 317
congenital ichthyosis, 85
epiphysial dysgenesis associated with cretinism in premature infant, *480
fibroblastic overgrowth of persistent tunica vasculosa lentis in infants born prematurely, 238
initial aerobic flora of newborn (premature) infants; nature, source and relation to ultraviolet irradiation and face masks, *89
medical social protection of, 490
relationship of congenital heart disease to premature birth, 411
Presentation: See Labor
Pringle-Bourneville's Disease: See Sclerosis, tuberous
Promin: See Tuberculosis
Propylene Glycol, effect on bacterial spores, 487
studies on air-borne infection in hospital ward; effects of ultraviolet irradiation and propylene glycol vaporization on prevention of experimental and air-borne infection of mice by droplet nuclei, 66
Protamine Insulin: See under Diabetes Mellitus
Proteins: See also Amino Acids; Nitrogen; etc.
deficiency anemia in infants; report of 2 cases, with associated temporary deficiency of antianemic factor in 1 and allergy and abnormal digestion of protein in other, *341
effect of high protein diets on size and activity of adrenal cortex in albino rat, 418
in Blood: See Blood, proteins
Prothrombin: See Blood, coagulation; Blood, prothrombin
Provitamin D_3: See Rickets
Pseudoxanthoma elasticum; angioid streaking of retina, 157
Psittacosis, virus pneumonias; pneumonias associated with known nonbacterial agents: influenza, psittacosis and Q fever, 150
Psychiatry, psychiatrist and behavior problem, 329
Psychology: See Mental Tests; Personality; etc.
Psychoses: See Nervous and Mental Disabilities; Neuroses and Psychoneuroses; etc.
Pubertas Praecox: See Puberty
Puberty: See also Adolescence
pubertas praecox (Pellizzi syndrome) in female infant caused by ventricular cyst, 497
Public Health: See Child Welfare; etc.
Puericulture: See Child Welfare
Puerperium: See Labor; Lactation; Pregnancy
Purpura fulminans (Waterhouse-Friderichsen syndrome): report of case with recovery, 329
Hemorrhagic: See also Diathesis, hemorrhagic

Purpura—Continued
hemorrhagic; chronic hemolytic anemia with paroxysmal nocturnal hemoglobinuria (Marchiafava-Micheli syndrome); report of case with marked thrombocytopenia in 5 year old child, 324
modern concepts of classification of hemorrhagic diatheses, 149
of Schoenlein-Henoch, 316
pneumococcic septicemia ending with Henoch's purpura (idiopathic nonthrombopenic purpura), 148
Pyemia, myocarditis in, *300
Pylorus, effect of hydrochloric acid on pyloric sphincter, on adjacent portions of digestive tract and on process of gastric evacuation, 75
Pyramidal Tract, new pyramidal sign of great frequency, 328
Pyrexia: See Fever
Pyrogens: See Fever
Pyuria: See under Urinary Tract

Q Fever: See Rickettsia
Quellung Reaction: See Pneumococci
Quinine, place in treatment of subtertian malaria, 322
Quinoline and Quinoline Derivatives, necrosis of islets of Langerhans produced experimentally (by styrl quinoline and alloxan), 415

Races: See Blood groups
Rachitis: See Rickets
Radiations: See Roentgen Rays; Ultraviolet Rays; and under names of various diseases
Radioactivity, secretion of radioactive sodium in human milk, 314
Ragweed: See Asthma; Hay Fever
Rapoport, M.: Electrocardiographic variations in acute glomerulonephritis, *106
Rations, ascorbic acid, riboflavin and thiamine content of cow's milk; influence of ration, *376
Reading, relationship between stuttering occurrence and grammatical factors in oral reading, 81
study of influence of communicative responsibility in choral speech situation for stutterers, 237
Reagin: See Anaphylaxis and Allergy
Recreation, progress in development of services for education and recreation, 316
Reese, M. K.: Initial aerobic flora of newborn (premature) infants; nature, source and relation to ultraviolet irradiation and face masks, *89
Reflex, functional development of fetal brain, 236
governing outflow of milk from breast, 226
new pyramidal sign of great frequency, 328
Refraction: See Eyes, accommodation and refraction
Reich, J. P.: Atypical poliomyelitis, 333
Reingold, I. M.: Myocarditis in children, *294
Reproduction: See also Pregnancy
dermatitis on synthetic ration adequate for growth and reproduction in rat, 314
effectiveness of linoleic, arachidonic and linolenic acids in reproduction and lactation, 58
Respiration, atelectasis complicating acute poliomyelitis with involvement of respiratory muscles, *457
Disorders: See also Asphyxia; Dyspnea
disorders; respiratory disturbances in newly born infant, 403
functional development of fetal brain, 236
physicochemical respiratory regulation and acid-base equilibrium in children, 79
Respiratory Quotient: See Metabolism
Respiratory Tract: See also Bronchi; Nose; etc.
acute laryngotracheobronchitis; treatment of obstructive laryngeal and tracheobronchial edema with hypertonic human plasma; preliminary report, 413
diseases; effect of tonsillectomy on respiratory infections in children, 150
diseases; incidence and mortality of breast and artificially-fed infants admitted to hospital with infections, 225
diseases; prevention of streptococcal upper respiratory infections and rheumatic recurrences in rheumatic children by prophylactic use of sulfanilamide, 320
diseases; respiratory disorders, 87
diseases; staphylococcic laryngotracheobronchitis, 235
Respiratory Tract—Continued
diseases; studies on control of acute infections of respiratory tract; results of sulfadiazine therapy from May 3, 1942 to May 2, 1943, *365
diseases; Weitmann reaction in respiratory diseases in children, 73
hemorrhage from trachea, bronchi and lungs of nontuberculous origin, 72
initial aerobic flora of newborn (premature) infants; nature, source and relation to ultraviolet irradiation and face masks, *89
laryngotracheobronchial diphtheria, 407
Reticuloendothelial System: See Jaundice; Liver; etc.
Retina, angioid streaking of, 157
angiomatosis retinae (von Hippel-Lindau disease); report on genealogic tree, 158
Retinochoroiditis, chorioretinitis associated with positive serologic tests for Toxoplasma in older children and adults, 329
Rh Factor: See Blood, groups; Blood, transfusion
Rheumatic Fever, acute, and valvular damage, 408
acute rheumatism, 68
clinical aspects of diagnosis of rheumatic disease, 67
comparison of Westergren and Kato erythrocyte sedimentation rate readings; relation to clinical status of children with rheumatic fever, *474
diagnosis of active rheumatism in childhood, 409
hypoprothrombinemia after salicylate administration in man and rabbits, 412
in children, 408
incidence of rheumatic stigmas in hearts which are usually considered nonrheumatic, 323
juvenile rheumatism; its problems, 232
medical and social measures in prophylaxis and treatment of rheumatic disease, 67
Mester's test in diagnosis of rheumatic disease of children, 233
present day concept of etiology and pathogenesis of rheumatic disease, 69
prevention of streptococcal upper respiratory infections and rheumatic recurrences in rheumatic children by prophylactic use of sulfanilamide, 320
prophylactic treatment of rheumatic disease in child, 68
rheumatic infections in Cincinnati hospitals; study of 3,475 admissions from 1930 to 1940; comparison with incidence in Philadelphia hospitals from 1930 to 1934, *182
rheumatic, myocarditis, *306
subcutaneous nodules in rheumatism, 409
Rheumatism: See Arthritis
Acute: See Rheumatic Fever
Rhinitis: See also Respiratory Tract, diseases
allergenic, due to Spanish moss, 421
Rhus, poisoning; oral prophylaxis against poison ivy; follow-up report, 84
poisoning; treatment by alcoholic extracts in small group controlled by preliminary patch tests, 84
Riboflavin: See also Pellagra; Vitamins, B
ascorbic acid and thiamine content of cow's milk; influence of ration, *376
induced riboflavin deficiency and riboflavin requirement of man, 402
slit lamp microscope in nutrition surveys, 227
toxicity and pharmacology of, 61
Ribs, diseases; case of Tietze's disease, 238
Rickets: See also Vitamins, D
activation of provitamin D_3 in rat, 227
Celiac: See Celiac Disease
effect of dietary fat on bone calcification in growing rat, 488
in Rio de Janeiro; cases observed in 1 year, 228
refractory to vitamin D shock therapy, 144
Renal: See Dwarfism
serum phosphatase activity and clinical rickets in children in Jerusalem, *348
treatment with massive doses of vitamin D, 228
vitellin, casein, liver and muscle tissue as sources of phosphorus for rachitic rat, 402
Rickettsia, virus pneumonias; pneumonias associated with known nonbacterial agents; influenza, psittacosis and Q fever, 150
Riga-Fede Disease: See Fibroma
Ringworm, experimental studies with dermatophytes; influence of age on allergic response in experimental ringworm in guinea pig, 239

Roentgen Rays, possible hazards of repeated fluoroscopies in infants, 86
Therapy: See under names of diseases, organs and regions, as Thorax; etc.
Roundworms: See Oxyuriasis
Rowland, V.: Subclinical vitamin deficiency; thiamine in skeletal muscle of infants and children, *30
Rubin, M. I.: Electrocardiographic variations in acute glomerulonephritis, *106
Russakoff, A. H.: Bleeding peptic ulcer in infancy, *384

Saccharides in Blood: See Blood sugar
Sachs-Tay Disease: See under Idiocy
Sage, D. N.: Oral moniliasis in newborn infants, *450
Salicyl Compounds, production of hypoprothrombinemia and hypocoagulability of blood with salicylates, 494
studies on prothrombin; prothrombinopenic effect of salicylate in man, 495
Salicylates: See Rheumatic Fever; Salicyl Compounds
Saliva, concentrations of sulfadiazine in human saliva attained by chewing paraffin containing sulfadiazine, 240
Salmonella: See also Bacteria, typhoid group; Food, poisoning
antigenic structure of bacteria incriminated in 4 unrelated outbreaks of food infection, 57
cerro; new type of Salmonella, 148
infections, epidemiologic aspects and laboratory diagnosis of, 232
sporadic infections caused by Salmonella suipestifer and Salmonella Oranienburg, 494
Saphir, O.: Myocarditis in children, *294
Pathologic changes in poliomyelitis, 333
Sarcoma: See under names of organs and regions
Saturnism: See Lead, toxicity
Scabies in children; diagnosis, complications and treatment, 422
treatment by T. E. T. M. S. [tetraethylthiuram monosulfide], 422
Scalp, symmetric nevi of face, tuberous sclerosis, epilepsy and fibromatous growth on scalp, with abnormal electroencephalograms of members of family, 330
Scarlatina: See Scarlet Fever
Scarlet Fever: See also Streptococci
myocarditis in, *298
scarlatinal encephalomyelitis, 230
surgical, 406
treatment, 147
Schick Test: See Diphtheria
Schönlein-Henoch Purpura: See Purpura
Schools: See also Universities
activity school and rural culture, 316
comparative studies of tuberculous infection in children in various districts of capital, 323
control of tuberculosis in children by prevention of its spread through contact, 323
dental services for school children of interior; ideas on organization and function of dentistry among school children, 500
height and weight measurements of school children, 316
necessity of introducing teaching of family pedagogy into higher grades of primary schools, into secondary schools, into normal schools for women and into maternity schools, 62
preventive activities of medical inspection in schools for combating problems of septic foci in school children, 316
report of speech survey, Holyoke, Massachusetts, 144
school attendance and child labor in United States, 403
sedimentation rate in school children of federal capital, 325
slit lamp microscope in nutrition surveys, 227
study of sound discrimination ability of elementary school pupils, 413
Schwartz, I.: Roentgenograms of chest taken during pertussis, *463
Scleredema: See Scleroderma
Sclerema: See Scleroderma
Scleroderma, acute sclerema, 404
Sclerosis, amyotrophic lateral; tocopherol level in human serum during oral tocopherol therapy, 489
multiple, and encephalomyelitis, 497
tuberous, symmetric nevi of face, epilepsy and fibromatous growth on scalp, with abnormal electroencephalograms of members of family, 330
Scrofula: See Tuberculosis
Sensitization: See under Anaphylaxis and Allergy; Immunity; etc.
Septicemia: See under organisms and diseases, as Pneumococci; etc.
Septum, Interventricular: See under Heart
Nasal: See under Nose
Serum: See Blood
Convalescent: See under Measles; Whooping Cough; etc.
Immune: See under Diphtheria; etc.
Sex, excretion of ketosteroids in human pregnancy urine in relation to sex of fetus, 403
Hormones: See Hormones
Shigella Dysenteriae: See Dysentery
Shock and acrolein; possible relationship of lipoid breakdown products to shock associated with burns, 499
Ombredanne's syndrome (postoperative shock) in infant after operation for torsion of cord, 155
Shoulder, bilateral congenital subluxation of acromioclavicular joint, 156
Siegel, M.: Studies on control of acute infections of respiratory tract; results of sulfadiazine therapy from May 3, 1942 to May 2, 1943, *365
Sigmoid: See also Colon; Intestines
infectious diseases with specific lesions of intestinal tract, 152
Silver Nitrate: See Teeth
Sinus, Thrombosis: See Thrombosis, sinus
Sinuses, Nasal; sinusitis and nasal allergy, 150
Sisto's Sign: See Crying
Skeleton: See Bones
Skin, Diseases: See Dermatitis; and under names of diseases, as Eczema; Herpes; Mycosis; etc.; and under names of plants, as Rhus; etc.
in vivo method for evaluation of germicidal substances used for skin disinfection, 85
manifestations of meningococcal infection, 230
moles and malformations of, 158
Reactions: See Anaphylaxis and Allergy; etc.
Skull: See Cranium
Slit Lamp: See under Conjunctiva; Cornea
Sluder Technic: See Tonsillectomy
Smallpox, effect of temperature on growth and survival of myxoma, herpes and vaccinia viruses in tissue culture, 56
effects of smallpox vaccination (vaccinia) on serologic tests for syphilis, 410
epidemic of 1797 in Mexico, 145
Francisco Xavier Balmis and introduction of vaccination to Latin America, 229
inhibiting effect of methionine, choline and betaine on rabbit's susceptibility to infection with vaccinia, 67
"something curious in medical line" (Benjamin Waterhouse and smallpox vaccination), 146
Social Conditions, influence on diphtheria, measles, tuberculosis and whooping cough in early childhood in London, 232
Societies, American Board of Pediatrics, Inc., 88, 241, 335, 503
eighth Pan-American Child Congress; its projection in America, 87
foreign, directory of, 162, 242, 336, 424, 506
international, directory of, 162, 242, 336, 424, 506
local, directory of, 164, 244, 338, 426, 508
national, directory of, 162, 242, 336, 424, 506
pediatric, directory of, 162, 242, 336, 424, 506
sectional, directory of, 163, 243, 337, 425, 507
state, directory of, 163, 243, 337, 425, 507

Society Transactions:

Chicago Pediatric Society, 332

Sodium Citrate: See Lead, toxicity
comparison of sodium and potassium metabolism of asthmatic and nonallergic children, 421
Diphenyl Hydantoinate: See Epilepsy
Radioactive: See Radioactivity
Sounds, study of sound discrimination ability of elementary school pupils, 413

Spanish Moss, allergenic rhinitis due to, 421
Spasm: See Convulsions; Epilepsy; etc.
Spaulding, E. B.: Oral moniliasis in newborn infants, *450
Speech: See also Voice
cardiovascular and metabolic study of stutterers and non-stutterers, 413
comparison of kinesthetic sensibility of speech-defective and normal-speaking children, 80
disorders and their treatment (relation to diseases of nervous system), 326
etiology of stammering, 150
functional speech and voice disorders, 150
importance of sensory training in speech therapy, 154
intelligence tests for deaf-mutes, 327
learning to speak after 6½ years of silence, 80
misarticulation and diadokokinesis in spastic paralytic, 497
official statistics of speech disorders encountered during World War I, 413
organized approach to therapy of stuttering, 81
phonographic scale for measurement of defective articulation, 413
relationship between stuttering occurrence and grammatical factors in oral reading, 81
report of speech survey, Holyoke, Massachusetts, 144
some social attitudes of group of 59 stutterers, 81
sound elements during first year of life; review of literature, 413
spastic, etiology and therapy of, 237
studies in psychology of stuttering; study of transfer of adaptation effect in stuttering, 237
study of influence of communicative responsibility in choral speech situation for stutterers, 237
study of onset and development of stuttering, 235
study of sound discrimination ability of elementary school pupils, 413
voice recordings, 413
working hypothesis as to nature and treatment of stuttering, 238
Spermatic Cord, Ombredanne's syndrome (postoperative shock) in infant after operation for torsion of cord, 155
Sphincter Muscles, achalasia of childhood, 152
Spinal Cord: See also Meninges; Nervous System; Pyramidal Tract; etc.
report of 6 cases of tumors occurring in childhood, 154
Spinal Fluid: See Cerebrospinal Fluid
Spinal Puncture, collapsed intervertebral disk following lumbar puncture, 499
Spine, collapsed intervertebral disk following lumbar puncture, 499
congenital narrowing of lumbosacral space, 497
Spirochaeta Pallida: See also Syphilis
spirochetal survival in frozen plasma, 70
Sprue, Nontropical: See Celiac Disease
Sputum cultures and gastric lavage, 410
Stains and Staining, enumeration and differentiation of leukocytes in counting chamber with propylene glycol-aqueous stains, 324
Stammering: See under Speech
Staphylococci, acute infection; further observations, 322
aureus, effect of pleural effusions on growth in vitro, 313
aureus, in milk of nursing mothers and alimentary canal of their infants, 225
aureus; study of humoral antibodies for Staphylococcus aureus in infants and their mothers, 408
cream-filled pastry source of infection, 414
initial aerobic flora of newborn (premature) infants; nature, source and relation to ultraviolet irradiation and face masks, *89
role of toxin and use of antitoxin in systemic staphylococcic infections, 408
staphylococcic laryngotracheobronchitis, 235
Status Asthmaticus: See Asthma
Epilepticus: See Epilepsy
Steatorrhea: See Celiac Disease
Steiner, P.: Mycotic endocarditis; report of case with necropsy; review of literature, *128
Sterilization: See also Germicides
surgical; observations on C T A B (cetavlon); its use in surgery, 500
Sternum, Puncture: See Bones, marrow
Still's Disease: See under Arthritis
Stillbirths: See Infant Mortality
Stillerman, M.: Attack rate and incubation period of measles; significance of age and of conditions of exposure, *15
Prophylaxis of measles with convalescent serum; principal factors influencing results, *1
Stomach: See also Gastrointestinal Tract; Pylorus
achlorhydric hypochromic microcytic anemia in child of 8 years, 234
acidity during first year of life, 328
acidity; hypochromic anemia in infancy, 149
depression of gastric motility without elevation of body temperature following injection of pyrogens, 74
effect of administration of vitamin B_1 on gastric secretion and motor activities of stomach; preliminary report, 61
effect of carminatives on emptying time of normal human stomach, 151
effect of hydrochloric acid on pyloric sphincter, on adjacent portions of digestive tract and on process of gastric evacuation, 75
gastric lavage and sputum cultures, 410
gastric lavage in control of treatment of pulmonary tuberculosis, 69
Ulcer: See Peptic Ulcer
Stomatitis aphthosa; treatment with nicotinic acid; 3 cases, 152
Stools: See Feces
Streptococci: See also Scarlet Fever
beta hemolytic streptococci isolated from public room floors, 57
chemotherapeutic effect of esters of penicillin, 502
chemotherapy by blocking bacterial nutrients; antistreptococcal activity of pantoyltaurine, 400
initial aerobic flora of newborn (premature) infants; nature, source and relation to ultraviolet irradiation and face masks, *89
milk-borne outbreaks due to serologically hemolytic streptococci, 493
prevention of streptococcal upper respiratory infections and rheumatic recurrences in rheumatic children by prophylactic use of sulfanilamide, 320
relation of neurotropic streptococci to encephalitis and encephalitic virus, 236
salivarius and other nonhemolytic streptococci of human throat, 327
serologic and biologic classification of hemolytic and nonhemolytic streptococci from human sources, 56
sore throat outbreak in upstate hospital, 412
sulfapyrazine; its activity against experimental infections with beta hemolytic streptococci as compared with that of sulfadiazine, sulfathiazole, sulfapyridine and sulfanilamide, 502
Stuttering: See under Speech
Styryl Quinoline: See Quinoline and Quinoline Derivatives
Sucrose, effect of glucose and sucrose on respiratory quotient and muscular efficiency of exercise, 58
Sugars: See also Carbohydrates; Dextrose; Lactose; etc.
in Blood: See Blood, sugar
in Urine: See Diabetes Mellitus
use of evaporated milk without added sugar for feeding of infants, *52
Sulfadiazine: See Sulfonamides; Tularemia
Sulfaguanidine: See Sulfonamides; Typhoid
Sulfamethazine: See Sulfonamides
Sulfathiazole: See Conjunctivitis; Measles; Meningitis; Sulfonamides
Sulfonamides, absorption and excretion of sulfamethyldiazine (2-sulfanilamido-4-methyl-pyrimidine) in human subjects, 86
acute nephritis and effect of sulfonamides on kidneys, 417
clinical experience with certain chemotherapeutic agents in treatment of various infectious diseases of childhood, 65
comparative effectiveness of arsenical compounds and sulfonamide drugs against bacterial infections, 408

Sulfonamides—Continued
comparative therapeutic activity of sulfonamides against bacterial infections in mice, 231
concentration of sulfadiazine in human saliva attained by chewing paraffin containing sulfadiazine, 240
effect of aromatic hydrocarbons on growth; reversible inhibition of pantothenic acid by sulfapyridine, 489
effect of continued sulfanilamide ingestion on acid-base equilibrium of dog, 501
evaluation of dangers of repeated administration of sulfadiazine and sulfathiazole in children, 501
fatal anuria following administration of sulfonamides with reference to tubular necrosis and regeneration, 417
infection and sulfonamide therapy in digestive disturbances and enteritis of infancy, 152
lesions in tissues of body following sulfonamide therapy, 501
local application of sulfanilamide to peripheral nerves, 240
mode of action; purines, amino acids, peptones and pancreas as antagonists and potentiators of sulfonamide in E. coli, 240
plasma prothrombin and liver function during sulfonamide therapy, 86
prevention of crystalluria during sulfadiazine therapy; experimental and clinical studies, 502
sensitization to sulfonamide compounds, 420
severe injury to kidneys and brain following sulfathiazole administration; high serum sodium and chloride levels and persistent cerebral damage, 500
studies on sulfonamide resistant organisms; origin of sulfonamide-resistant pneumococci, 331
sulfadiazine, 159
sulfamethazine; clinical trials in children, 240
sulfamethazine (2-4′-aminobenzenesulfonyl-amino-4: 6-dimethylpyrimidine); new heterocyclic derivative of sulfanilamide, 331
sulfanilamide bacteriostasis in presence of mercuric chloride and *p*-aminobenzoic acid, 501
sulfapyrazine; its activity against experimental infections with beta hemolytic streptococci as compared with that of sulfadiazine, sulfathiazole, sulfapyridine and sulfanilamide, 502
sulfapyridine bacteriostasis of Lactobacillus arabinosus and its counteraction, 502
susceptibility of Shigella paradysenteriae to sodium sulfathiazole and sulfaguanidine in vitro, with some information regarding Eberthella typhosa, Salmonella paratyphosa, Escherichia coli, Salmonella morgani and proteus, 408
therapeutics of sulfonamide compounds; importance of study of their concentration in body, 159
Therapy: See also Bacteria; Communicable Diseases; Conjunctivitis; Diarrhea; Diphtheria; Dysentery; Gastrointestinal Tract; Gonorrhea; Intestines; Measles; Meningitis; Otitis Media; Pneumonia; Respiratory Tract, diseases; Rheumatic Fever; Whooping Cough; etc.
therapy in infancy, 160
therapy in nutritional disturbances, 144
Sulfur metabolism of children, 58
Suprarenal Preparations: See Adrenal Preparations
Suprarenals: See Adrenals
Surgery: See also Apparatus; etc.
surgical scarlet fever, 406
Syphilis: See also Neurosyphilis; and under names of organs and regions, as Cardiovascular Diseases; etc.
congenital, antiquity (described as leprosy), 145
congenital, cardiovascular involvement in, 410
congenital, clinical importance of Sisto's sign in early diagnosis of, 148
congenital, unrecognized, 323
effects of smallpox vaccination (vaccinia) on serologic tests for, 410
Hereditary: See Syphilis, congenital
Kahn verification test in malaria (differential diagnosis of syphilis), 408
liver extract in arsenical intolerance, 240
nonspecific serologic reactions, 70
report on flocculation test of Mazzini, 410

T. E. T. M. S.: See Scabies
Tachycardia: See Heart, rate
Tannin, toxicity of tannic acid, 240
Tapeworm Infection, Diphyllobothrium latum in Florida, 408
Tay-Sachs Disease: See under Idiocy
Teeth: See also Dentistry
caries-fluorine hypothesis and suggested study to test its application, 500
dangerous effects of vitamin D overdosage on dental and paradental structures, 488
dental caries as influenced by fat versus carbohydrate in diet, *278
dental services for school children of interior; ideas on organization and function of dentistry among school children, 500
domestic water and dental caries, 85
endemic fluorosis in Great Britain, 401
experiments on dental lesions of glandular origin, 156
fingersucking; serial dental study from birth to 5 years, 159
fluorine distribution, 315
localized vertical growth disturbance, 488
preventive activities of medical inspection in schools for combating problems of septic foci in school children, 316
some disorders of dentition period, 500
treatment of caries in children with silver nitrate, 500
Temperature: See also Cold; Fever; Heat; etc.
determination of rate of thyroid hormone secretion at various environmental temperatures, 419
effect on growth and survival of myxoma, herpes and vaccinia viruses in tissue culture, 56
Testes, surgical treatment of severe orchitis in mumps, 147
undescended; cryptorchidism, 329
Tetanus, fatal effects of prolonged complete curarization, *360
immunity induced by third dose of toxoid 3 years after basic immunization, based on study of 38 allergic children, *22
toxoid; its use in United States Army, 493
Tetany, disturbed kidney function in newborn infant associated with decreased calcium: phosphorus ratio, 404
due to deficiency in magnesium; its occurrence in child of 6 years with associated osteochondrosis of capital epiphysis of femur (Legg-Perthes disease), *117
Tetracaine Hydrochloride: See Anesthesia
Tetraethylthiuram Monosulfide: See Scabies
Thalhimer, W.: Attack rate and incubation period of measles; significance of age and of conditions of exposure, *15
Prophylaxis of measles with convalescent serum; principal factors influencing results, *1
Thaysen-Gee Disease: See Celiac Disease
Thiamine: See also Vitamins, B
ascorbic acid and riboflavin content of cow's milk; influence of ration, *376
effect of administration of vitamin B_1 on gastric secretion and motor activities of stomach; preliminary report, 61
excretion tests in children with paralytic poliomyelitis, 318
subclinical vitamin deficiency; thiamine in skeletal muscle of infants and children, *30
Thorax: See also Heart; Lungs; Pleura; Ribs; etc.
mumps with edema of chest, 317
roentgenograms of chest taken during pertussis, *463
vibration of thorax by percussion of skull and patella, 159
Thorium X: See Nevi
Threadworms: See Parasites
3,3′-Methylenebis (4-Hydroxycoumarin): See Coumarin
Throat: See also Larynx; Otorhinolaryngology; Tonsils; etc.
milk-borne outbreaks due to serologically hemolytic streptococci, 493
sore throat outbreak in upstate hospital, 412
Staphylococcus aureus in milk of nursing mothers and alimentary canal of their infants, 225
Streptococcus salivarius and other nonhemolytic streptococci of human throat, 327
Thrombin: See Blood, coagulation
Thrombocytosis: See Purpura
Thrombopenia: See under Purpura, hemorrhagic

Thrombophlebitis, Sinus: See Thrombosis, sinus
Thromboplastin: See Blood, prothrombin
Thrombosis, sinus; thrombophlebitis of cavernous sinus, 496
Thyroid: See also Parathyroid
determination of rate of thyroid hormone secretion at various environmental temperatures, 419
Diseases: See Goiter, exophthalmic
effect of chloride with high and low iodine supply on thyroid gland of rat, 419
experiments on dental lesions of glandular origin, 156
Hypothyroidism: See also Cretinism
hypothyroidism; mental development of congenitally hypothyroid children; its relationship to physical development and adequacy of treatment, *205
hypothyroidism; serum phosphatase values in children showing retardation in osseous development and low metabolic rates, 420
relation to mammary gland structure in rat with reference to male, 155
relationship of thyroid to polyuria of experimental diabetes insipidus, 419
Ticks: See also Encephalitis; Encephalomyelitis; Tularemia
transient paralysis due to bite of American dog tick (Dermacentor variabilis Say), *126
Tietze's Disease: See Ribs, diseases
Tissue: See Cells
Adipose: See Fat; Obesity
Staining: See Stains and Staining
Tocopherol: See Vitamins, E
Tomatoes, availability for human nutrition of vitamin C in raw cabbage and home-canned tomato juice, 402
Tonsillectomy and acute nephritis, 82
and poliomyelitis; new concept of etiologic relationship, 406
complications of, 327
effect on respiratory infections in children, 150
Tonsillitis: See Tonsils
Tonsils, preventive activities of medical inspection in schools for combating problems of septic foci in school children, 316
Toomey, J. A.: Levinson ratio and tryptophan test; comparative value in diagnosis of tuberculous meningitis, *469
Poliomyelitis; results of treatment during acute stages of disease, *393
Torrey, J. C.: Initial aerobic flora of newborn (premature) infants; nature, source and relation to ultraviolet irradiation and face masks, *89
Tourniquets: See Hemostasis
Toxin and Antitoxin: See under Diphtheria; Scarlet Fever; Tetanus; Whooping Cough; etc.
Toxoid: See under Diphtheria; Tetanus; etc.
Toxoplasmosis, chorioretinitis associated with positive serologic tests for Toxoplasma in older children and adults, 329
fetal toxoplasmic encephalitis; type of congenital cerebral disease, 78
in wild rats, 320
Transfusion: See Blood, transfusion
Treponema: See Spirochaeta Pallida
Trichostrongylidae, effect of various stages of vitamin A deficiency in white rat on resistance to Nippostrongylus muris, 315
Tryparsamide, nutritional degeneration of optic nerve in rats; its relation to tryparsamide amblyopia, 238
Tryptophan Test: See Cerebrospinal Fluid
Tubercle Bacilli: See Tuberculosis
death of tubercle bacilli subjected to oxygen deprivation in presence of moisture and of warmth, 57
Tuberculin: See under Tuberculosis
Tuberculosis: See also under names of organs, regions and diseases, as Bones; Meninges; Pleura; etc.
asphyxiated bacteria as vaccine in, 70
bronchial obstruction and pulmonary atelectasis, 233
clinical episode in tuberculosis and meteorologic environment, 69
combating in Union of Socialist Soviet Republics, 322
comparative studies of tuberculous infection in children in various districts of capital, 323
congenital, 233
Tuberculosis—Continued
control in children by prevention of its spread through contact, 323
correlation of extent with amount of polysaccharide in serum, 323
disappearance of tuberculin reaction in children under treatment for allergies, 322
experimental, inhalation of nebulized promin in, 148
histopathology of Mantoux reaction and erythema nodosum, 148
in adolescents and young adults, 233
index of children in Uruguay, 148
influence of social conditions on diphtheria, measles, tuberculosis and whooping cough in early childhood in London, 232
management of minimal tuberculous lesion, 69
milk policy for children, 402
modern trends in prevention and social aspects of, 410
myocarditis in, *307
obstructive emphysema and atelectasis in tuberculosis of infants and children, 323
prognostic blood tests in, 410
pulmonary calcification and tuberculin sensitivity among children in Williamson County, Tennessee, 410
pulmonary; first infection from roentgenologic and anatomic point of view, 70
pulmonary; gastric lavage and sputum cultures, 410
pulmonary, gastric lavage in control of treatment, 69
rupture of large cavern in course of pneumothorax, 70
transitory fleeting pulmonary shadows, 151
Tularemia, activity of sodium sulfadiazine against Bacterium tularense; effect on growth in vitro, 313
activity of sodium sulfadiazine against Bacterium tularense; treatment of experimental tularemic infection in chick embryo, 313
reaction of chick embryo to virulent and nonvirulent strains of Bacterium tularense, 314
tularemic meningitis; report of case and summary of previously reported cases, *44
Tumors: See Angioma; Cancer; Chondroma; Fibroadenoma; Fibroma; Ganglioneuroma; Hemangioma; etc.; and under names of organs and regions, as Brain; Breast; Spinal Cord; etc.
Twins, identical, allergy in; report on 7 pairs of twins, 84
identical, similar urogenital anomalies in, *199
Typhoid, infectious diseases with specific lesions of intestinal tract, 152
outbreak due to small colony variety of Eberthella typhosa, 494
protective action of Vi bacteriophage in Eberthella typhi infections in mice, 320
two cases treated with sulfaguanidine, 321

Ulcers: See under names of organs and regions
Peptic: See Peptic Ulcer
Ultraviolet Rays: See also under names of organs and diseases
activation of provitamin D_3 in rat, 227
bactericidal action of ultraviolet radiation on air-borne organisms, 56
initial aerobic flora of newborn (premature) infants; nature, source and relation to ultraviolet irradiation and face masks, *89
studies on air-borne infection in hospital ward; effect of ultraviolet light on cross-infection in infants' ward, 66
studies on air-borne infection in hospital ward: effects of ultraviolet irradiation and propylene glycol vaporization on prevention of experimental and air-borne infection of mice by droplet nuclei, 66
studies on air-borne virus infections, 321
Umbilicus, Hernia: See Hernia, umbilical
Undulant Fever, artificial fever therapy in brucellosis, 321
Universities, calcium, phosphorus and nitrogen metabolism of young college women, 59
Urea, clearance; diodrast and inulin clearances in nephrotic children with supernormal urea clearances, 417
clearance; renal function with new nomographic method for determination of urea clearance, 329

Urethra, occlusion of urethral meatus, *275
Urinary Tract: See also Genitourinary Tract; Kidneys; etc.
achalasia in children, 82
Urination, incontinence; possible cure for enuresis, 417
incontinence; relationship between infantile enuresis and epileptic crisis, 81
Urine: See also Diuresis and Diuretics; Pregnancy, urine in; Urination; under names of diseases; etc.
absorption, excretion and distribution of penicillin, 501
effect of sodium citrate administration on excretion of lead in urine and feces, 331
estimation of "true" ascorbic acid in, 489
evaluation of nicotinic acid nutrition by studies of urinary excretion, 61
organic acids; biochemical lesion of lysine deficiency in man, 314
phosphorus; urinary excretion and serum concentration of inorganic phosphate in man, 400
prevention of crystalluria during sulfadiazine therapy; experimental and clinical studies, 502
steroids; excretion of ketosteroids in human pregnancy urine in relation to sex of fetus, 403
suppression; fatal anuria following administration of sulfonamides with reference to tubular necrosis and regeneration, 417
therapeutics of sulfonamide compounds; importance of study of their concentration in body, 159
Uvea, anomalous processes of ciliary type on posterior surface of iris, 157
displacement of ciliary processes to posterior surface of iris, 157

Vaccination: See Immunity; and under names of various diseases, as Smallpox; Typhoid; etc.
Vaccines: See Whooping Cough
Vaccinia: See Smallpox
Varicella: See Chickenpox
Variola: See Smallpox
Vegetables: See Fruits and Vegetables
Venereal Diseases: See Gonorrhea; Neurosyphilis; Syphilis
Ventilation, radiant heat and comfort, 62
Vertebrae: See Spine
Vestibular Apparatus: See Ear
Vibration of thorax by percussion of skull and patella, 159
Virilism: See Adrenals
Viruses: See also Distemper; Encephalitis; Encephalomyelitis; Herpes; Influenza; Measles; Pneumonia; Poliomyelitis; etc.
identification of 2 strains isolated from cases of atypical pneumonia, 72
studies on air-borne virus infections, 321
virus pneumonia, 235
Vision: See also Blindness; Eyes; etc.
defective; epitome of agnosia, apraxia and aphasia with proposed physiologic-anatomic nomenclature, 154
testing in Illinois, 330
Vital Statistics: See Infant Mortality
Vitamins: See also Ascorbic Acid; Nicotinic Acid; Riboflavin; Thiamine
A absorption and its relation to intestinal motility in fibrocystic disease of pancreas, 76
A absorption in infantile eczema, 422
A absorption test in cases of giardiasis, *189
A deficiency; effect of various stages in white rat on resistance to Nippostrongylus muris, 315
A; effect of bone dysplasia on cranial nerves in vitamin A deficient animals, 315
A, factors influencing level in blood of rats, 60
A; hypervitaminosis A and carotenemia, *33
A; influence of lecithin feeding on fat and vitamin A absorption in man, 401
A; influence on serum lipids of normal and deficient rats, 61
A; minimum requirements in infants as determined by vitamin A concentration in blood, 402
and artificial feeding, 60
B: See also Nicotinic Acid; Riboflavin; Thiamine
B; chemotherapy by blocking bacterial nutrients; antistreptococcal activity of pantoyltaurine, 400
B complex of peeled wheat bread, 315
B; effect of aromatic hydrocarbons on growth; reversible inhibition of pantothenic acid by sulfapyridine, 489
Vitamins—Continued
B; effect of pantothenic acid deficiency on blood lipoids of dog, 58
B; mechanism of Kenny method and its correlation with vitamin B therapy in poliomyelitis, 229
B; use of B complex in treatment of infantile eczema, 331
B_1: See Thiamine
B_2: See Riboflavin
C: See Ascorbic Acid
D: See also Rickets
D; dangerous effects of overdosage on dental and paradental structures, 488
D; factors influencing retention of nitrogen and calcium in period of growth; calcium and vitamin D requirements of older child, *265
D; rickets refractory to vitamin D shock therapy, 144
D, treatment with massive doses of, 228
Deficiency: See also Rickets; etc.; and under specific vitamins
deficiency in diabetic children, 155
E: See also Lactation; Pregnancy; Reproduction
E, biologic determination of, 489
E; serum tocopherol; its relation to failure of vitamin E therapy for pseudohypertrophic muscular dystrophy, *371
E; tocopherol level in human serum during oral tocopherol therapy, 489
E; treatment of diseases of muscle, 238
K: See also Blood, coagulation
K and neonatal hemorrhage, 87
K; hemorrhagic disease of newborn, 228
K in hemorrhagic disease of newborn infant, 228
K; prothrombin studies; effect of vitamin K on hypoprothrombinemia induced by dicumarol [dicoumarin] in man, 234
K requirements of newborn, 228
nonspecific therapy in anterior poliomyelitis; preliminary report on use of vitamins B and E and artificial fever, 318
subclinical deficiency; thiamine in skeletal muscle of infants and children, *30
use in clinical neurology, 227
value of dairy products in nutrition, 488
vitamin therapy today, 227
Vocabulary: See under Speech
Voice, functional speech and voice disorders, 150
recordings, 413
Vollmer Patch Test: See Tuberculosis

Waddell, W. W., Jr.: Influenzal meningitis, *194
War: See also Aviation and Aviators; Military Medicine; etc.
anemia in women and children on wartime diets, 234
effect on maternal welfare program in Illinois, 315
nutritional anemia in children and women; wartime problem, 325
protection of children in danger zones and planning for care of children after evacuation arising from military necessity, 316
review of cases of celiac disease in hospital for sick children since outbreak of war, 415
Wassermann Reaction: See Syphilis
Water, domestic, and dental caries, 85
hypothetical relationship of water supplies to poliomyelitis, 491
metabolism in sick and healthy infants, 315
Waterhouse, Benjamin; "something curious in medical line" (Benjamin Waterhouse and smallpox vaccination), 146
Waterhouse-Friderichsen Syndrome: See Adrenals, hemorrhage
Watson, E. H.: Hydranencephaly; report of 2 cases which combine features of hydrocephalus and anencephaly, *282
Weber-Christian Disease: See Panniculitis
Wedum, A. G.: Rheumatic infections in Cincinnati hospitals; study of 3,475 admissions from 1930 to 1940; comparison with incidence in Philadelphia hospitals from 1930 to 1934, *182
Wedum, B. G.: Rheumatic infections in Cincinnati hospitals; study of 3,475 admissions from 1930 to 1940; comparison with incidence in Philadelphia hospitals from 1930-1934, *182
Weight: See Children; Obesity
Weinglass, A.: Fatal effects of prolonged complete curarization, *360

Weissman, N.: Subclinical vitamin deficiency; thiamine in skeletal muscle of infants and children, *30
Weltmann Reaction: See Blood, coagulation
Wenner, H. A.: Complications of infantile eczema caused by virus of herpes simplex; description of clinical characteristics of unusual eruption and identification of associated filtrable virus, *247; correction, 503
Wertz, A. W.: Ascorbic acid, riboflavin and thiamine content of cow's milk; influence of ration, *376
Westergren Method: See Blood, sedimentation
Wheat Germ Oil: See Vitamins, E
Whitehead, B. W.: Influenzal meningitis, *194
Whooping Cough, active immunization by intranasal route in experimental pertussis, 65
airplane altitude flights in, 147
clinical results with use of agglutinogen from phase I Haemophilus pertussis as skin test for susceptibility to, 405
influence of social conditions on diphtheria, measles, tuberculosis and whooping cough in early childhood in London, 232
Lederle's pertussis antigen in treatment; report of investigation, 492
Whooping Cough—Continued
myocarditis in, *298
pertussis toxin, 229
polyneuritis in patient with, 148
relation between amounts of pertussis antigen injected and production of agglutinins, 405
reported morbidity and mortality in United States, 406
roentgenograms of chest taken during pertussis, *463
studies with Hemophilus pertussis; comparative antigenic analysis of Bacillus parapertussis and Hemophilus pertussis, phase I, with consideration of clinical significance. 64
treatment, 147
vaccines, 406
Wile, S. A.: Myocarditis in children, *294
Wolf, A. M.: Clinical aspects of poliomyelitis, 332
Worms: See Tapeworm Infection

X-Rays: See Roentgen Rays

Zeldes, M.: Epiphysial dysgenesis associated with cretinism in premature infant, *480
Zona: See Herpes

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CONTENTS

PAGE

Initial Stabilization of the Diabetic Child. Lieutenant Commander John Mitchell Brush (MC), U. S. N. R. 429

Erythroblastosis Fetalis: A Proposed Definition and Clarification of the Term. Madge Thurlow Macklin, M.D., London, Ontario, Canada 445

Oral Moniliasis in Newborn Infants. Nina A. Anderson, M.D.; Dorothy N. Sage, M.S., and E. H. Spaulding, Ph.D., Philadelphia 450

Atelectasis Complicating Acute Poliomyelitis with Involvement of Respiratory Muscles. M. Cooperstock, M.D., Marquette, Mich... 457

Roentgenograms of the Chest Taken During Pertussis. Jerome L. Kohn, M.D., and Irving Schwartz, M.D., New York; Lieutenant (jg) Jerome Greenbaum (MC), U.S.N., and Mary M. I. Daly, M.D., New York 463

The Levinson Ratio and the Tryptophan Test: Comparative Value in the Diagnosis of Tuberculous Meningitis. Frederic A. Kriete, M.D.; Harold C. Epstein, M.D., and John A. Toomey, M.D., Cleveland 469

Prophylactic Value of Sulfathiazole Against Neonatal Gonococcic Conjunctivitis. Morris Gleich, M.D.; Marvin L. Blumberg, M.D., and Alvin S. Mason Jr., M.D., New York 472

Comparison of Westergren and Kato Erythrocyte Sedimentation Rate Readings: Relation to the Clinical Status of Children with Rheumatic Fever. John B. McKinley, M.S., and Robert L. Jackson, M.D., Iowa City 474

Case Reports:

Epiphysial Dysgenesis Associated with Cretinism in a Premature Infant. Maurice L. Blatt, M.D.; Mary Zeldes, M.D., and James Goodfriend, M.D., Chicago 480

Pneumococcic Meningitis: Complete Recovery of a Six Month Old Infant Treated with Penicillin. Abraham M. Litvak, M.D.; Emanuel Appelbaum, M.D., and Morton Greene, M.D., Brooklyn 485

Abstracts from Current Literature 487

News and Comment 503

Book Reviews 504

Directory 506

General Index 511